ECOG-ACRIN
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SUMMARY OF CHANGES

Amendment 2, version April 30, 2014

NCI Protocol #: ACRIN 6698
Local Protocol #: ACRIN 6698

NCI Version Date: April 30, 2014
Protocol Date: April 30, 2014

#	Global Changes
1	Reference to ACRIN has been updated to appropriately reflect ECOG-ACRIN or ACR resources supporting the study.
2	References to the —Adverse Event Expedited Reporting System (AdEERS)" have been changed to —CTEP Adverse Event Reporting System (CTEP-AERS)" throughout the protocol.
3	Reference to Appendix I: Informed Consent Form Template has been deleted throughout; this section has been removed from the current document and introduced into a separate Word document complete with consent form-only Summary of Changes.

#	Section /Links	Page(s)	Change
1	Cover Pages	2	The date of Amendment #2 has been introduced. The versioning history information has been transferred from the second of the cover pages to the first.
2	CTSU Instructions	3	CTSU Address and Contact Information has been added.
3	Table of Contents	4-5	Has been updated.
4	6.2	14	New section: —Access Requirements" for CTEP-IAM and CTSU have been added.
5	6.2	14-15	The following language has been added (*italics*) or deleted (~~strikethrough~~) – ~~—~~*Prior to the recruitment of a patient for this study, investigators must be registered members of the Cancer Trials Support Unit (CTSU). Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on CTEP Web site: http://ctep.cancer.gov/investigatorResources/investigator_registration.htm or by calling the PMB at (240) 276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.* *Each CTSU investigator or group of investigators at a clinical site must*

			also obtain IRB approval for this protocol and submit IRB approval and the supporting documentation listed in the previous paragraph to the CTSU Regulatory Office before they can enroll patients. *All forms and documents required for this study can be downloaded from CTSU members" area of the website (https://www.ctsu.org). Patients can be registered only once all eligibility criteria have been met, and the study site is listed as „approved" inthe CTSU RSS.* ~~All regulatory documentation must be submitted to ACRIN Headquarters (via fax: 215-717-0936, ATTN: ACRIN Protocol Development and Regulatory Compliance Department).~~ All institutions must have study-specific, initial full-board Institutional Review Board (IRB) approval for the protocol and informed consent form (ICF). ~~A supplemental Informed Consent Form Template is included in this protocol as Appendix I and may be adjusted for local IRB submission.~~ The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB overseeing the study for the site. ~~A copy of the IRB approval letter, a copy of the IRB approved, site-specific ICF, ACRIN Statement of Investigator, Federalwide Assurance documentation, and evidence of completion of the Protecting Human Research Participants training from the National Institutes of Health Office of Extramural Research (or institution-specific equivalent) must be delivered to the trial monitor to review the approved form and to keep on file at ACRIN Headquarters prior to activation of the study at the local site.~~ ***Requirements for ACRIN 6698 site registration:*** *• CTSU IRB Certification* *• CTSU IRB/Regulatory Approval Transmittal Sheet* ***Pre-study requirements for patient enrollment on ACRIN 6698*** *• Patient must meet all inclusion criteria, and no exclusion criteria should apply* *• Patient has signed and dated all applicable consents and authorization forms* *• Site must meet institution requirements as noted in Section 6.1"*
6	7.1.1	15	ACRIN ―6698" has been specified, and reference to ―ACRIN's Clinical Trials Management System (CTMS)" has been added.
7	7.2	15	A new header has been added: ―Participant Registration" and subsequent sections have been renumbered.
8	7.2.1	15	The following language has been added (*italics*) or deleted (~~strikethrough~~) – ―Upon successful registration to the ISPY 2 TRIAL, participants who consented to the ACRIN 6698 DW-MRI study must be registered *through OPEN* ~~via the ACRIN website at https://clinicalweb1.phila.acr.org/ClinicalAcrin/faces/jsp/index.jsp. Upon registration, an ACRIN case-specific calendar will be generated and sent to the site. This calendar lists all forms, reports, and images required by protocol along with form due dates at ACRIN's Data Management Center (DMC). The calendars are available 24 hours a day on the ACRIN website and will be updated as the study proceeds to reflect data that have been received, due dates for queries about unclear~~

			~~data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling. The investigative site is required to submit data according to protocol as detailed on each participant's ACRIN calendar~~."
9	7.2.2	15-16	All language in this section is new.
10	7.3 and 7.3.1	16	A new header has been added, and subsequent sections have been renumbered. For Section 7.3.1, introductory text has been revised to read: ~~"~~*Upon successful participation registration in OPEN, sites transition to the ACRIN.ORG web site to submit study data.* ~~To submit data via the ACRIN web site,~~ *T*he appropriate investigator-designated research staff …"
11	10.10.2.1	27	The telephone number for the AEMD Help Desk has been added and the CIP– SAE Reporting Line has changed from (301) 897-1704 to (301) 897-7402.
12	10.10.3	28	2nd paragraph: The AdEERSMD helpline is now referred to as the AEMD helpline. The contact information has not changed.
13	10.10.3	28	3rd paragraph: All language in this section has been replaced.
14	14	30	Former Section 14.1 and final paragraph in now-Section 14.1 (Audits): Reference to the ACRIN Monitoring program and to NCI CIP audit procedures have been deleted as ACRIN now adheres to ECOG-ACRIN and CTMB requirements for auditing under NCI CTEP and the National Clinical Trials Network. Final paragraph under 14.3: Has been deleted; this paragraph references submission of IRB materials to ACRIN. Current procedures mandate approval-submissions via CTSU RSS.

ECOG-ACRIN

ACRIN 6698

Diffusion Weighted MR Imaging Biomarkers for Assessment of Breast Cancer Response to Neoadjuvant Treatment: A sub-study of the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis)

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Original Date: February 29, 2012
Activation Date: August 27, 2012
Version Date: April 30, 2014
Administrative Update #1: October 28, 2013
Includes Amendments 1 - 2

Limited Participation:
Participation in the ACRIN 6698 study is limited to I-SPY 2 TRIAL institutions.

Current I-SPY 2 Site Locations:

- Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA
- Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
- University of Minnesota Medical Center, Minneapolis, MN
- University of Colorado Cancer Center, Aurora, CO
- Moores Cancer Center, University of California, San Diego, La Jolla, CA
- Inova Health System, Falls Church, VA
- The USC/Norris Comprehensive Cancer Center, The University of Southern California, Los Angeles, CA
- Arizona Cancer Center, The University of Arizona, Tucson, AZ
- Cardinal Bernardin Cancer Center, Loyola University Health System, Maywood, IL
- The Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC
- Mayo Clinic, Scottsdale, AZ
- Mayo Clinic, Rochester, MN
- OHSU Knight Cancer Institute, Oregon Health and Science University, Portland, OR
- Swedish Cancer Institute, Swedish Medical Center, Seattle, WA
- The Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX
- The University of Chicago Cancer Research Center, Chicago, IL

CONFIDENTIAL

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Data collection will be performed in the ACR's Clinical Trials Management System (CTMS):**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	Please refer to the Forms Completion Guidelines for the Forms Submission Schedule.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility or treatment-related questions Contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

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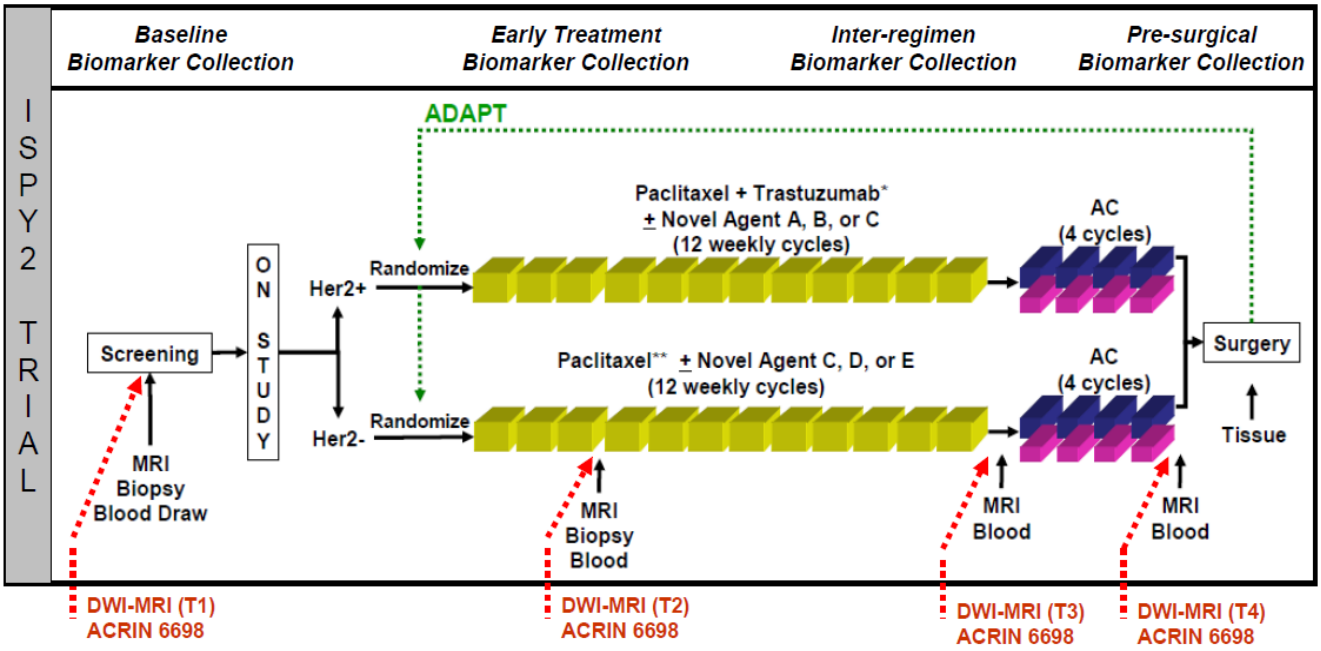
ECOG-ACRIN

ACRIN 6698

Diffusion Weighted Magnetic Resonance Imaging Biomarkers for Assessment of Breast Cancer Response to Neoadjuvant Treatment: A sub-study of the **I-SPY 2 TRIAL** (**I**nvestigation of **S**erial Studies to **P**redict **Y**our **T**herapeutic **R**esponse with **I**maging **A**nd mo**L**ecular Analysis)

FIGURE 1: SCHEMA



STUDY OBJECTIVES/SPECIFIC AIMS

Primary objective:
To determine if the change in tumor apparent diffusion coefficient (ADC) value measured from each treatment time point to baseline using diffusion-weighted MRI (DW-MRI) is predictive of pathologic complete response

Secondary objectives:
To determine if the combined measurement of change in tumor ADC value, change in tumor volume and change in peak signal enhancement ratio (SER) is predictive of pathologic complete response (pCR)

To investigate the relative effectiveness of the individual measurements, change in tumor ADC value, change in tumor volume, and change in peak signal enhancement ratio (SER) for predicting pathologic complete response in experimental treatment arms

To assess the test-retest reproducibility of ADC measurements by DW-MRI applied to breast tumors

ELIGIBILITY

Women who are eligible to participate in the I-SPY 2 TRIAL may participate in the ACRIN 6698 imaging study.

SAMPLE SIZE

The ACRIN 6698 sample size estimate is based on enrollment of 404 patients from all experimental arms from the I-SPY2 TRIAL.

1. ABSTRACT

This protocol for human research study is conducted according to United States and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (e.g. Title 45, Part 46 Code of Federal Regulations) and the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) research policies and procedures.

The objective of ACRIN 6698 study is to determine if diffusion weighted magnetic resonance imaging (DW-MRI) is effective for measuring breast tumor response to neoadjuvant treatment and if response measured by DWI early in the course of taxane-based therapy is predictive of pathologic response. ACRIN 6698 will be performed as a sub-study to the ongoing I-SPY 2 breast cancer neoadjuvant treatment trial. MRI is included in the I-SPY 2 protocol as a measurement method for tumor response, based on data from ACRIN 6657/I-SPY 1 showing higher predictive value of tumor volume by MRI than diameter measurement by any method, including clinical exam, mammography, and MRI (Hylton et al. 2012). Change in tumor volume, measured at multiple time points during treatment, is used to update the patient randomization schema as the trial progresses. A basic DWI acquisition was included as part of the I-SPY 2 MRI exam in anticipation of an imaging science companion protocol. While the basic DWI protocol may provide information about DWI assessment of response to treatment, it is sub-optimal as a quantitative imaging biomarker. ACRIN 6698 protocol will specifically address the question of DWI sensitivity to drug effects via alterations in tumor water mobility, and will directly compare DWI-MRI to dynamic contrast-enhanced MRI (DCE-MRI) measurements of tumor microvascular behavior. ACRIN 6698 imaging protocol will include the necessary elements for a high quality, quantitative imaging study, including protocol specification, monitoring and quality control, image processing and contextual data analysis.

2. BACKGROUND AND SIGNIFICANCE

Functional MRI techniques for measuring breast tumor response to treatment

Magnetic resonance imaging (MRI) of the breast is a sensitive method for assessing both tumor morphology and physiology. The most common technique for functional assessment of breast tissue is based on DCE-MRI and involves the serial acquisition of MR images before, and at multiple points following intravenous injection of gadolinium contrast agent. By fitting DCE-MRI data to an appropriate pharmacokinetic model, DCE-MRI allows noninvasive, in vivo measurement of physiological parameters related to tissue perfusion, microvascular permeability, and extracellular/extravascular volume fraction. These measurements can be used to characterize tumor neovascularization and can detect changes in tumor vascular properties resulting from treatment.

A number of recent studies have applied DCE-MRI to measure breast cancer response to neoadjuvant chemotherapy. These studies have evaluated MRI both for ability to detect and measure residual disease as well as ability to predict clinical or pathologic response endpoints and recurrence-free survival. The majority of studies have been performed in small series of patients and have found changes in DCE-MRI parameters measured early in treatment to be associated with response outcomes. Johansen *et al* (2009) evaluated DCE-MRI for early prediction of response to neoadjuvant chemotherapy (NAC) and five year survival in patients with locally advanced breast cancer. In this study, area under the curve (AUC) was calculated from DCE-MRI time-intensity curves and compared to clinical treatment response. Relative

signal intensity and AUC were reduced after only one cycle of NAC in patients with clinical treatment response. In Ah-see *et al* (2007), DCE-MRI was performed after two NAC cycles and correlated to final clinical and pathological response. DCE-MRI parameters included transfer constant (K^{trans}), rate constant (k_{ep}), leakage space (v_e) ,maximum Gd-DTPA concentration (Max Gd), relative blood volume (rBV), and relative blood flow (rBF), with change in K^{trans} found to be the best predictor of pathologic non-response. Yu *et al* found different results when investigating the value of using three parameters (tumor size, K^{trans}, and k_{ep}) obtained after the first treatment cycle in predicting the final clinical response following neoadjuvant anthracycline and cyclophosphamide chemotherapy. In this small study (n=29), early tumor size change by MRI was a better response predictor than either K^{trans} or k_{ep}. In another small study (n=30), Martincich *et al* (2004) showed DCE-MRI performed best after two weeks of NAC showing that tumor volume reduction after two cycles had the strongest predictive value.

DWI of the breast

Diffusion-weighted imaging (DWI) is an alternative MRI technique that can be used to measure the mobility of water molecules in vivo. DWI is sensitive to tissue characteristics such as cell density, membrane permeability, and microstructure. As such, DWI provides different but complementary biologic information about tumors and their response to treatment. In DWI, the MRI signal is sensitized to water diffusion using varying levels of a magnetic field gradient. DWI sequences are available on most current MRI scanners and are easily acquired as part of the patient exam in addition to standard DCE-MRI, with little time penalty. DWI studies of the breast have shown decreased diffusivity in malignant breast lesions (Guo, Cai et al. 2002; Sinha, Lucas-Quesada et al. 2002; Woodhams, Matsunaga et al. 2005), primarily attributed to the increased cell density associated with breast tumors. DWI has also been used to evaluate response to treatment. Separate studies have found that the apparent diffusion coefficient (ADC) in tumors increases in response to treatment earlier than detectable changes in tumor size or vascularity measured by DCE-MRI (Chenevert, Stegman et al. 2000; Theilmann, Borders et al. 2004; Pickles, Gibbs et al. 2006; Sharma, Danishad et al. 2009). The increase in ADC is thought to be due to cell death and necrosis, and may be a valuable early indicator of treatment efficacy. Indeed, a growing number of studies have found ADC measures to be predictive of breast cancer treatment outcome. In separate studies, baseline ADC was lower in clinical responders versus non-responders (Iacconi, Giannelli et al. 2009; Park, Moon et al. 2010; Li, Cheng et al. 2011), and change in ADC with treatment was significantly greater in responders (Iacconi, Giannelli et al. 2009; Park, Moon et al. 2010), even after only the first cycle of chemotherapy (Sharma, Danishad et al. 2009; Li, Cheng et al. 2011). In prediction of pathologic response, Fangberget et al further showed mid-treatment ADC was higher in patients who ultimately achieved a pathologic complete response (pCR) compared to those with residual disease (Fangberget, Nilsen et al. 2010). On the other hand, ADC was not predictive of clinical response in several other studies, whether measured prior to therapy or mid-treatment (Manton, Chaturvedi et al. 2006; Nilsen, Fangberget et al. 2010; Woodhams, Kakita et al. 2010). These disparate findings may be attributable to differences in DWI methods, analysis approaches, or study populations. Further larger studies are needed to validate the use of ADC as a predictive biomarker.

Rationale for Selected Approach and Trial Design

The objective of the proposed ACRIN 6698 study is to determine if DW-MRI is effective for measuring breast tumor response to neoadjuvant treatment. ACRIN 6698 will evaluate DWI in the context of the ongoing I-SPY 2 breast cancer trial and will add to the knowledge gained in the first phase (I-SPY1/ACRIN 6657) about the effectiveness of DCE-MRI for assessing

neoadjuvant response. ACRIN 6698 will evaluate ADC alone, and in comparison to measurements of tumor vascularity obtained by DCE-MRI. Because cellularity and vascularity represent different but complementary aspects of tumor biology, evaluation using both DWI and DCE techniques may be more informative and potentially more effective than either alone for characterizing breast cancers and their response to treatment.

Integration with I-SPY 2: Serial MRI exams are already required procedures for tumor volume measurement in I-SPY 2. Implementation of ACRIN 6698 will require only the addition of a DWI measurement to each patient scan. This can be accomplished at minimal cost, with minimal added risk, and with minimal added inconvenience to patients. The timing of the four MRI exams (at baseline, early in the course of taxane-based therapy, between taxane-based and anthracycline regimens and between completion of neoadjuvant treatment and surgery) allows exploration of a number of important questions regarding the sequencing and effectiveness of neoadjuvant treatment. Baseline information can be both prognostic and predictive of response, risk of recurrence and survival. Early time point information has the potential to inform rapid assessment and modification to the treatment approach. Inter-regimen and pre-surgical measurements allow taxane-based and anthracycline-based therapies to be assessed individually; the pre-surgical measurement gives a final assessment of response and is useful for surgical planning as well. Quantitative imaging performed at each of these time points and for all patients and experimental arms will provide a rich database for evaluating DWI.

ACRIN 6698 Study activation and patient enrollment: ACRIN 6698 will utilize many elements of study activation and patient enrollment already in place as part of I-SPY 2. Twenty sites are activated for patient enrollment under I-SPY 2; all of these sites have met qualification requirements for basic imaging. All patients accrued to I-SPY 2 are currently receiving MRI exams at the four protocol time points needed for ACRIN 6698. ECOG-ACRIN and the 6698 PI‘s institution (UCSF) are currently providing imaging core services to the I-SPY 2 trial; therefore procedures for image acquisition, transmittal, image analysis and reporting are already in place. Additional requirements for ACRIN 6698 activation will include DWI qualification (submission of phantom and patient data using the advanced DWI protocol) and modification to the existing 6657 case report process to include DWI-specific documentation. As with ACRIN 6657/I-SPY 1, a single consent form will be used to enroll patients to ACRIN 6698/I-SPY 2. This will involve an appendix to the existing, approved, I-SPY 2 protocol and consent form. I-SPY 2 TRIAL investigators have developed a process to amend the master protocol for the addition or removal of new candidate molecules. This same process will be used to amend the protocol for inclusion of ACRIN 6698 and for changes requested by the Cancer Therapeutics Evaluation Program.

Patient benefits and safeguards: Consideration of patient benefits and safeguards has been integral to the development and implementation of I-SPY 2. The I-SPY 2 advocate team works closely with the network of investigators to develop processes and informational materials describing the I-SPY 2 trial to patients, as well as its potential benefits and risks. Benefits and risks include those associated with randomization and experimental treatments, as well as those associated with MRI exams. The requirement for multiple MRI exams has not been a barrier to accrual for either I-SPY 1 or I-SPY 2. Since activation of ACRIN 6698 will require only an additional 10-15 minutes of scan time added to the required MRI exams, we do not anticipate any accrual barriers beyond those already encountered in I-SPY 2 in general. I-SPY 2 tracks the number and reasons for patients who decline and accept participation.

Selection of pathologic complete response (pCR) as the primary endpoint: In the ACRIN 6698 study, pCR will be used as the primary endpoint as recent studies have shown that pCR is predictive of recurrence-free survival, particularly when evaluated within intrinsic breast cancer subtypes (Esserman L. et al., 2011; Huober J. et al, 2010; Straver ME et al, 2010; Esserman L et al, in press). pCR remains to be validated as a surrogate marker. With a lack of alternative short-term endpoints, pCR as the endpoint for the primary analysis appears to be the best choice. However, the subtypes of all tumors will be known and potential alternative endpoints including residual cancer burden (RCB), Ki-67 and other immunohistochemical markers and gene expression signatures will be collected for all patients enrolled. Therefore it will be possible to evaluate imaging results against other outcomes at the time of analysis.

A number of tissue and serum-based markers are being evaluated as part of the master I-SPY 2 protocol, and are selected on the basis of their likelihood to predict response to systemic therapy, their robustness and reproducibility, and their potential as therapeutic targets. Markers being evaluated included several associated with cell cycle checkpoints (Cyclin D1, Cyclin E, P21, P27), proliferation (MCM2, Ki-67, DNA index), angiogenesis (CD34) and apoptosis (Bcl-2, p53). Receptor tyrosine kinases and downstream genes (Her-2 neu, Topo II, EGRF), molecular profiles (CGH, gene expression arrays) and tissue proteomic arrays are also being evaluated. Specifically, markers of genetic instability, cell cycle progression and cellular proliferation are being explored as predictors for anthracycline responsiveness, and markers of apoptotic potential as predictors for taxane responsiveness.

3. STUDY OBJECTIVES/SPECIFIC AIMS

The objective of the proposed ACRIN 6698 study is to determine if DW-MRI is effective for measuring breast tumor response to neoadjuvant treatment. ACRIN 6698 will evaluate DWI in the context of the ongoing I-SPY 2 breast cancer trial and will add to DCE-MRI for assessing neoadjuvant response. ACRIN 6698 will evaluate ADC alone, and in comparison to measurements of tumor vascularity obtained by DCE-MRI. Because cellularity and vascularity represent different but complementary aspects of tumor biology, evaluation using both DWI and DCE techniques may be more informative and potentially more effective than either alone for characterizing breast cancers and their response to treatment.

3.1 Primary Aim

3.1.1 To determine if the change in tumor ADC value measured from each treatment time point to baseline is predictive of pathologic complete response

3.2 Secondary Aims

3.2.1 To determine if the combined measurement of change in tumor ADC value, change in tumor volume and change in peak SER is predictive of pathologic complete response

3.2.2 To investigate the relative effectiveness of the individual measurements, change in tumor ADC value, change in tumor volume, and change in peak signal enhancement ratio (SER) for predicting pathologic complete response in experimental treatment arms

3.2.3 To assess the test-retest reproducibility of ADC metrics applied to breast tumor

4. STUDY OVERVIEW

I-SPY2 is a breast cancer treatment trial and uses an adaptive phase 2 design to evaluate targeted drugs in the setting of neoadjuvant therapy. Under the I-SPY2 schema (Figure 1), patients are screened initially to identify those with high risk of recurrence according to the Mammaprint 70-gene signature. Low risk patients do not continue on the trial. Included patients are randomized to one of several sub-arms testing either paclitaxel alone or paclitaxel in combination with an investigational new drug, selected on the basis of phase I safety data and preliminary evidence of efficacy in the Her2+ or Her2- population. Following the taxol-based regimen, all patients continue to standard chemotherapy with doxorubicin and cyclophosphamide. As part of the adaptive design of I-SPY 2, change in tumor volume measured by MRI at serial time points during chemotherapy is used to adjust the randomization schema as the trial proceeds. I-SPY2 opened in March 2010 and is currently enrolling patients at 19 sites.

As part of the ACRIN 6698 study, diffusion-weighted (DW) MRI will be performed prior to DCE-MRI at each time point prescribed in I-SPY2. Measurements of the apparent diffusion coefficient (ADC) from DW-MRI images will be tested alone and in combination with DCE-MRI parameters for ability to predict pathologic response.

5. PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

Patients participating in I-SPY 2 at sites that have met ACRIN 6698 site qualification requirements are eligible to participate. Patient eligibility criteria for ACRIN 6698 include all I-SPY 2 TRIAL inclusion and exclusion criteria. Patients enrolling in I-SPY 2 and agreeing to participate in ACRIN 6698 as part of the I-SPY 2 consenting process must also be co-enrolled to ACRIN 6698 via the ACRIN website: https://clinicalweb1.phila.acr.org/ClinicalAcrin/faces/jsp/index.jsp.

5.1 Inclusion Criteria

5.1.1 Meets I-SPY 2 TRIAL inclusion criteria

5.1.2 Able to tolerate imaging required by protocol

5.2 Exclusion Criteria

5.2.1 Does not meet I-SPY 2 trial inclusion criteria

5.3 Recruitment and Screening

All patients participating in the ACRIN 6698 study will be recruited from the master I-SPY 2 TRIAL. All I-SPY 2 TRIAL sites are eligible to participate in the ACRIN 6698 imaging study.

Patient eligibility will be systematically assessed at each of the participating I-SPY 2 study sites. The I-SPY 2 TRIAL screening log will be kept documenting the review of potentially eligible patients as well as reasons for non-enrollment. Sites will provide detailed information to all relevant treating physicians on the conduct of the trial to optimize physician participation. Monthly conference calls will review recruitment at each site so that sites not meeting the I-SPY 2 recruitment goals of 6 patients per site per year can be identified early and interventions to improve recruitment can be instituted. ECOG-ACRIN will participate in these teleconferences to help identify any obstacles in participating in the advanced imaging study.

ACRIN 6698 will be registered on Clinicaltrials.gov. The master I-SPY 2 TRIAL is also listed on the NIH website Clinicaltrials.gov to enable referring physicians to identify local sites for patient referral (NCT01042379). Patients will also be able to find the I SPY-2 TRIAL sites

through breastcancertrials.org, a clinical trial matching web site. Women diagnosed with breast cancer can go to this national-service web site and enter their information to find clinical trials appropriate for them. Once they find a trial, they can contact a research site and send their information through TRIAL CONNECT, which includes their contact information and their eligibility screened against the trial eligibility. In addition, the study will work with advocate groups across the country to improve awareness.

A large, organized cadre of experienced patient advocates will participate within community patient support services locations to help educate patients about the trial and assist in the recruitment and retention process for the I-SPY 2 TRIAL. These advocates will be experts on the trial design and conduct and will assist potentially eligible patients in understanding the informed consent process as well as assisting those enrolled in navigating the various steps within the trial assessment and treatment process.

ECOG-ACRIN will develop materials to aid participant recruitment. All materials used for participant recruitment will be reviewed and approved by each institution‘s Institutional Review Board (IRB).

5.4 Inclusion of Women and Minorities

Women of all ethnic groups are eligible for this trial. Based on the demographic information from the I-SPY 1 TRIAL, we expect 19% participation of African American women, 4% Asian, and 2% other. The following information will be reported in compliance with FDA annual reporting requirements.

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993, with regard to inclusion of women and minorities in clinical research, the projected gender and minority accruals are shown in Table 1 below:

Table 1: Gender and Minority Accrual Estimates

Racial and Ethnic Categories	**Females**	**Total**
Hispanic or Latino	40	40
Not Hispanic or Latino	364	364
Ethnic Category: Total of all subjects	**404**	**404**
Racial Category		
American Indian or Alaskan Native	5	5
Asian	20	20
Black or African American	85	85
Native Hawaiian or other Pacific Islander	5	5
White	289	289
Racial Category: Total of all subjects	**404**	**404**

6. SITE SELECTION

6.1 Institution Requirements

The potential sites for this study are I-SPY 2 TRIAL participating institutions that meet ACR Imaging Core Laboratory qualifications for participating in this study. All I-SPY 2 sites already

have an ACRIN Institutional Participants Committee (IPC)-approved General Qualifying Application (GQA) on file. In addition, each institution submitted a Protocol Specific Application (PSA), which documents that sites have the necessary personnel, equipment, and referral base to carry out the requirements specific to the I-SPY 2 and ACRIN 6698 protocol. The GQA and PSA can be found on the ACRIN web site at www.acrin.org/6698protocol.aspx.

Sites also must obtain DW-MRI qualification for the scanner(s) that will be used for scanning trial participants. In addition, test images of the DW-MRI scan per protocol specifications (see Section 9.0) must be reviewed and approved prior to participant enrollment. All scanner and image qualification materials are available at www.acrin.org/6698imagingmaterials.aspx, and Section 9.0 provides detailed information regarding the DW-MRI imaging protocol and related procedures.

6.2 Access Requirements

Site personnel will be required to obtain CTEP-IAM (Clinical Therapy Evaluation Program-Identity and Access Management) log-in credentials to access the portals for site and roster profiling within the Cancer Trials Support Unit (CTSU), site approval for enrollment (CTSU RSS-the Regulatory Support System), and participant registration (via OPEN-the Oncology Patient Enrollment Network). For more information about CTEP-IAM credentialing, see the CTSU Web site FAQs: https://www.ctsu.org/readfile.aspx?fname=public/ctep-iam_factsheet.pdf. Data collection will continue according to the outline under Data Management in Section **Error! Reference source not found.**.

6.3 Regulatory Requirements and Documentation

Prior to the recruitment of a patient for this study, investigators must be registered members of the Cancer Trials Support Unit (CTSU). Each investigator must have an NCI investigator number and must maintain an ―active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on CTEP Web site: http://ctep.cancer.gov/investigatorResources/investigator_registration.htm or by calling the PMB at (240) 276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must also obtain IRB approval for this protocol and submit IRB approval and the supporting documentation listed in the previous paragraph to the CTSU Regulatory Office before they can enroll patients.

All forms and documents required for this study can be downloaded from CTSU members' area of the website (https://www.ctsu.org). Patients can be registered only once all eligibility criteria have been met, and the study site is listed as ‗approved' in the CTSU RSS.

All institutions must have study-specific, initial full-board Institutional Review Board (IRB) approval for the protocol and informed consent form (ICF). The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB overseeing the study for the site.

Requirements for ACRIN 6698 site registration:

- CTSU IRB Certification

- CTSU IRB/Regulatory Approval Transmittal Sheet

Pre-study requirements for patient enrollment on ACRIN 6698
- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- Site must meet institution requirements as noted in Section 6.1.

6.4 Accrual Goals and Monitoring

Accrual to ACRIN 6698 will, in large part, be dependent upon accrual to the I-SPY 2 TRIAL. The ECOG-ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 404 participants. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving recruitment barriers.

ECOG-ACRIN leadership regularly reviews the overall trial accrual and may request information about a trial‘s accrual performance to better understand general accrual barriers or issues. Accrual and safety information will be presented to the ECOG-ACRIN Data and Safety Monitoring Committee (DSMC) at regularly scheduled meetings.

7. SUMMARY OF DATA SUBMISSION

7.1 General

7.1.1 All ACRIN 6698 data forms will be entered through ACR‘s Clinical Trials Management System (CTMS) Data Center. The web address is www.acrin.org.

7.2 Participant Registration

7.2.1 Upon successful registration to the ISPY 2 TRIAL, participants who consented to the ACRIN 6698 DW-MRI study must be registered through OPEN.

7.2.2 **Registration**: All site staff (Lead Group) will use OPEN to enroll participants to this study. OPEN can be accessed at https://OPEN.ctsu.org or from the CTSU members' web site OPEN tab. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All participants have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. Information on establishing a CTEP-IAM account can be found at https://www.ctsu.org/readfile.aspx?fname=public/ctep-iam_factsheet.pdf

  This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.

- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent "Registrar" role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under Regulatory Support System (RSS) on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.
- Once the patient is successfully registered to the OPEN system, sites will receive an e-mail notification from ECOG-ACRIN containing the 6698 case number and calendar.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

7.3 Clinical Data Submission Via ACR CTMS Portal

7.3.1 Upon successful participant registration in OPEN, sites transition to the ACRIN.ORG web site to submit study data. The appropriate investigator-designated research staff will log in to the Data Center through the ACRIN web site with the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, out of range, or in the wrong format (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 move to the next data element. 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 form will remain available on the web until the "Complete Form" button is depressed.

7.3.2 Once data entry of a form is complete, and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form" button on the form summary screen and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

7.3.3 If technical problems prevent access to the Data Center website, sites will be unable to enter data. The site RA or investigator should notify the DMC if a problem with the Data Center is encountered. All sites will be notified through an ECOG-ACRIN/CTSU broadcast message when access to the web data entry is unavailable and the estimated time when access will be restored. The investigative site should wait until access is restored to submit data.

7.4 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system is controlled by a sequence of identification codes and passwords.

7.5 Electronic Data Management

7.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server; the data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Biostatistics and Data Management Center (BDMC) that are more comprehensive than those built into the web-based data entry screens. The BDMC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. The validation program generates a log of errors which is managed by the DMC Data Manager (DM). The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time DMC spends resolving problems. All communication with the participating sites is handled by the DMC.

7.4.2 If missing or problematic data is detected, the DM sends an Additional Information Request (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DM updates the participant‘s data submission calendar with the Z1 due date to notify the site RA or investigator of when a response is expected. The calendar will be updated upon receipt of the query response.

7.6 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. This report lists data items (e.g. forms, reports, and images) that are delinquent. It is distributed at regular intervals via the electronic mail system to both the RA and the investigator at each site. 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 RA and/or investigator. Future Forms Due Reports may be sent on an as-needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool. At any time, sites may run their own Forms Due Reports using the Site Operations Tool on the ACRIN website.

7.7 Data Quality Assurance

7.6.1 The Biostatistics Center (BC) at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are

drawn directly from the permanent database at the DMC. The transfer of data between the DMC and the BC have been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to the DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

7.6.2 Data will be monitored to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the DMC will contact the site to resolve the problem. Protocol Development and Regulatory Compliance (PDRC) will be involved in this process as needed. If the BDMC and PDRC cannot reconcile the problem with the site, it will be brought to the ECOG-ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

8. STUDY PROCEDURES

8.1 Time Point 1: Pre-treatment MRI (T1)

8.1.1 Obtain a signed informed consent form for I-SPY 2 TRIAL that includes informed consent to participate in ACRIN 6698;

8.1.2 Complete the registration and screening of I-SPY 2 TRIAL patients;

8.1.3 Perform DW-MRI (T1) scan prior to contrast administration for DCE-MRI scan during the baseline imaging session;

8.1.4 Perform repeat DW-MRI scan for reproducibility aim prior to contrast administration (if patient had consented to participate in DW-MRI scan-rescan);

8.1.5 Perform assessment of Adverse Events (AEs).

8.2 Time Point 2: Early treatment DW-MRI (T2)

8.2.1 Perform DW-MRI (T2) scan prior to contrast administration for DCE-MRI scan at the end of week 3 of paclitaxel regimen, prior to the fourth paclitaxel infusion;

8.2.2 Perform repeat DW-MRI scan for reproducibility aim prior to contrast administration (if not performed at T1 and patient had consented to participate in DW-MRI scan-rescan);

8.2.3 Perform assessment for AEs.

8.3 Time Point 3: Inter-regimen MRI (T3)

8.3.1 Perform DW-MRI (T3) scan prior to contrast administration for DCE-MRI scan prior to starting AC treatment;

8.3.2 Assessment for AEs.

8.4 Time Point 4: Pre-Surgery MRI (T4)

8.4.1 Perform DW-MRI (T4) scan prior to contrast administration for DCE-MRI scan following completion of the patient‘s neoadjuvant chemotherapy and prior to surgery;

8.4.2 Assessment for AEs.

8.5 Follow up

Patients will be followed for five years as part of the I-SPY 2 TRIAL. There is no follow up associated with the ACRIN 6698 trial.

8.6 Off Study Criteria

Participants will be considered off study if they do not meet master I-SPY 2 TRIAL requirements or are unable to complete the pre-treatment DW-MRI imaging series.

8.7 Study Procedures Table

Table 2 Study Procedure	Time Point 1 Pre-treatment (T1)	Time Point 2 Early Treatment (T2)	Time Point 3 Inter-regimen (T3)	Time Point 4 Pre-surgery (T4)
Informed Consent Form	X			
Screening/Eligibility Review	X			
Pre-Registration Imaging Review	X			
Study DW-MR Imaging[1] (done prior to DCE-MRI)	X[1]	X[1]	X[1]	X[1]
Repeat DW-MRI scan	X[2]	X[2]		
AE Assessment	X	X	X	X

[1]: All ACRIN 6698 DW-MR imaging should be performed prior to contrast administration for DCE-MRI scan and should be performed on same day.

[2]: A subset of patients will receive a repeat DWI scan. This scan may occur at imaging time point T1 or imaging time point T2.

9. IMAGING PROTOCOL

9.1 Imaging Requirements and Parameters

MRI Procedures:

The breast MRI protocol includes a T2-weighted sequence, diffusion-weighted imaging sequence, and dynamic contrast-enhanced (DCE) series. The general imaging parameters are listed below. DCE-MRI will be performed using a bilateral, 3D, fat-suppressed, T1-weighted gradient echo sequence with 80-100 second temporal resolution. DWI will be performed bilaterally using a multi-b value echo planar technique. The ACRIN 6698 Imaging Manual contains the DW-MR imaging protocol with all imaging procedures and parameters and is available on the ACRIN 6698 website at www.acrin.org.

DWI will be acquired prior to dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) using a diffusion-weighted spin–echo echo planar imaging sequence. All vendors (GE, Philips, Siemens, Toshiba) offer commercial versions of diffusion-weighted sequences. Scanning will be performed in the axial orientation, with diffusion gradients applied in three orthogonal directions to measure isotropic ADC. The sequence will employ parallel imaging (reduction factor = 2) and fat suppression. The optimal technique for fat suppression (SPAIR, STIR, etc.) may vary between scanners. DWI will be performed using multiple b-values including 0, 100, 600 and 800 s/mm^2. The general sequence parameters are given in Table 2 of the Imaging Manual. The maximum number of slices that can be acquired during a single acquisition is typically 24-30 slices and coverage should be adjusted to keep the scan within a single acquisition to minimize scan time and motion artifacts. Total scan time for the DWI sequence should be under 5 minutes.

DWI Reproducibility Scan

Reproducibility of ADC measurements will be evaluated by performing ―test-retest" DWI scans for a subset of patients. The test-retest procedure will be performed by acquiring two DWI scans using identical scan protocols, prior to injection of contrast agent. Patients will be required to leave and return to the scan table between DWI scans. Full repositioning of the patient and retuning of the MRI system will simulate procedures of an entirely distinct MRI session. Test-retest scans will only be performed at one MRI visit. It is preferable for this to be performed at baseline; however, test-retest can be performed at the early treatment time point (visit 2).

Magnet Field Strength

There is no theoretical dependence of ADC on field strength, although differences may arise related to field inhomogeneity effects, signal-to-noise and severity of artifacts. To maximize accrual, both 1.5T and 3T field strengths will be allowed in 6698. However, it will be required that all sequential exams for a given patient are performed on MRI systems with the same field strength and model (currently required in I-SPY-2). Information regarding field strength will be collected and effects of field strength will be explored at the time of data analysis.

Image Processing and Analysis

Serial changes in ADC (in units mm^2/s) measured from b = 0 and 800 s/mm^2 DW images will be evaluated in the primary breast tumor over the course of treatment. Sites will perform tumor ADC measurements according to the region-of-interest (ROI) measurement procedures described below. ADC maps generated from b = 0, 800 s/mm^2 DW images and screen capture images showing ROI placement will be submitted in addition to originally acquired data to ECOG-

ACRIN Diagnostic Imaging Headquarters in Philadelphia following each MRI exam. A list of the data required for transmission for each study case is given in Table 3 of the Imaging Manual.

Primary tumor ADC measurement: Whole tumor ROI methods will be used to calculate tumor ADC at each treatment time point. An ROI will be drawn over the largest solid tumor region, with tumor size and location determined from corresponding DCE-MRI images. Care should be taken to avoid necrotic, cystic, or adipose tissue by referencing to T1- and T2-weighted images and ADC maps in defining the ROIs. Tumor ROIs will typically include areas of low diffusivity, reflected by hyperintensity on DWI with low ADC on corresponding ADC map. A screen capture should be saved in each case to illustrate ROI placement for reporting. ROIs will be adjusted to changing tumor size and shape in serial examinations (and positioned over the remaining area of solid tumor).

Alternative tumor ADC metrics: Additional image processing and ADC analysis will be performed by the centralized core facility to explore alternative ADC metrics. Traditional ADC measurement includes b=0 data in the fitted b-value range, although this increases the influence of flow and perfusion on ADC. Alternatively, a minimum b-value of 100s/mm^2 in the fitted b-value range effectively removes perfusion signal (Bogner et al, 2009; Padhani et al, 2009). Perfusion-sensitive ADC (calculated from b = 0 and 800 s/mm^2 DW images) and perfusion-insensitive ADC (calculated from b = 100 and 800 s/mm^2 DW images) will be derived from each DWI dataset. In addition, high-ADC cystic tissues that may exist in breast lesions prior to start of therapy may mask incremental therapy-induced necrosis within solid tumor. Analysis of the low-ADC portion of the ADC histogram (e.g. ADC<1.5x10-3mm^2/s) is hypothesized to enhance sensitivity to therapy-induced alteration of solid tumor constituents of the lesion. Low-ADC metrics will also be analyzed and evaluated.

Site Qualification and Quality Control

As part of the existing site qualification process for I-SPY 2, all sites are required to submit two breast MRI cases acquired using the DCE-MRI protocol described above. Qualification scans are reviewed by the ACR Imaging Core Lab for both compliance and image quality, as part of a core service agreement with I-SPY 2. Approval of the qualification scans is required for I-SPY 2 trial activation.

In addition to the existing image qualification process for I-SPY 2, sites enrolling on ACRIN 6698 will be required to perform phantom QC testing and submit two DWI cases from human subjects acquired using the multi-b value sequence outlined in Table 2 of the Imaging Manual. The DWI data from both QC and patient scans must meet specific quality criteria (e.g., artifacts, distortion, signal-to-noise ratio) for acceptance. Qualification must be performed for each scanner used for I-SPY 2 patients and must be repeated after any major scanner upgrade or change of breast coil.

Regular quality-control (QC) scans will be performed at each site using a standardized phantom to evaluate consistent DWI performance. DWI scans for submitted study cases will be reviewed by the ACR Imaging Core on a regular basis for ongoing QC, and if artifacts or inconsistencies are identified the site will be contacted to help resolve the problem.

For additional details regarding site qualification process and QC measures, please refer to the ACRIN 6698 Site Imaging Manual.

9.2 Images Submission

Each participating site is required to submit all acquired I-SPY 2 and ACRIN 6698 MRI imaging of study patients to the ACR Imaging Core laboratory via TRIAD-OA, which provides a validated, secure method of electronic image transmission. The TRIAD software anonymizes, encrypts, and applies lossless compression to the images before they are transferred to the ECOG-ACRIN image archive in Philadelphia, PA. Prompt submission of all image data is essential to ensure adequate quality control. Images should be transmitted along with an Imaging Transmittal Worksheet (ITW) that can be found on the ACRIN 6698 web site at: www.acrin.org/6698imagingmaterials.aspx. For TRIAD support contact the representatives of the core lab via email at Triad-Support@phila.acr.org or by phone: 215-940-8820.

Instructions for image submission and anonymization, as well as information regarding Quality Control of images, are available at www.acrin.org/6698_imagingmaterials.aspx.

10. ADVERSE EVENTS REPORTING

Adverse events will be monitored and reported as documented in the I-SPY 2 protocol. However, adverse events reported for the imaging component of the trial, DW-MRI, will be monitored and managed by ECOG-ACRIN.

10.1 Definition of Adverse Event

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological 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). Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

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

A pre-existing condition is one that is present at the start of the study. A pre-existing medical condition is defined as an AE if the frequency, intensity, or character of the medical condition worsens during the study period. At screening visit, any clinically significant findings/abnormalities should be recorded as a pre-existing condition. At the end of study, any new clinically significant findings/abnormalities that meet the definition of an AE must be documented as AEs.

10.2 Definition of Serious Adverse Event

A **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
- Is a congenital anomaly/birth defect, or
- Requires intervention to prevent any of the above, per the investigator/sponsor.

Life-Threatening Adverse Event: A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

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

10.3 Adverse Event Grading

Grade denotes the severity of the AE. An AE is graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0:

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

A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).

10.4 Adverse Event Attribution

Attribution is used to determine whether an AE is related to a study treatment or procedure.

Attribution categories are:

Definite: The AE is **clearly related** to a treatment or procedure
Probable: The AE is **likely related** to a treatment or procedure
Possible: The AE **may be related** to a treatment or procedure
Unlikely: The AE is **likely unrelated** to a treatment or procedure
Unrelated: The AE is **clearly not related** to a treatment or procedure

10.5 Expected and Unexpected Adverse Events

AEs may be **expected** or **unexpected**:

- An **expected AE** is one that is described in the protocol, the ICF, or the investigator‘s clinical brochure.
- An **unexpected AE** is one that has not been described in the protocol, the ICF, or the investigator‘s clinical brochure.

10.6 Expected DW-MRI Related Adverse Events

The DW-MRI scan is performed without the use of an imaging agent. As such, there are no known expected AEs for DW-MRI. However, the following are expected AEs associated with MRI.

10.6.1 Expected Adverse Events Associated With MRI

- Anxiety/stress;
- Claustrophobia;
- Discomfort.

Because of the powerful magnetic force of the MRI scanner, the patient may be ineligible to participate in the study if she has:

- Metallic or other surgical implants (for example: pacemaker, heart valves, aneurysm clips, metal plates or pins and some orthopedic prostheses);
- Metal pieces in your eye(s) or other body part(s).

10.7 Source Documentation of Adverse Events

At each contact (study visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on AEs through discussion and, as appropriate, by examination. All expected (Section 10.6) and unexpected AEs considered possibly, probably, or definitely related with the severity level of grades 3, 4, 5 that occur within 30 days of the DW-MRI will be documented and reported in the study participant's chart and AE CRFs to ensure compliance with the reporting requirements of ECOG-ACRIN and the National Cancer Institute's (NCI) Clinical Trials Network. See Table A below for additional details. Local IRBs and/or institutions may stipulate additional AEs reporting based upon their review of the protocol.

IMPORTANT: Recording of AEs on source document does not constitute reporting. Please ensure that AEs are documented in the participant's chart and an AE CRF in order to satisfy routine reporting requirements; AEs and SAEs are reported to ECOG-ACRIN and NCI per protocol-specific reporting requirements.

All unresolved AEs should be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the AEs are otherwise explained. Any death or AE occurring at any time after a participant has discontinued or terminated study participation that may be reasonably related to the study imaging effect should be reported.

10.8 Reporting of Adverse Events

Prompt reporting of AEs is the responsibility of each investigator, clinical RA, and/or nurse engaged in clinical research. Anyone uncertain about whether a particular AE should be reported should contact ACRIN headquarters at **(215) 717-2763** for assistance. However, an AE report should be submitted if there is a reasonable suspicion of the medical treatment or imaging procedure.

All unresolved AEs should be followed by the principal site investigator until the AE is resolved, otherwise explained, or the site has documented due diligence in attempting to procure the requisite medical records.

Any death or AE occurring at any time after a participant has discontinued or terminated study participation that may be **reasonably related** to the DW-MRI should be reported.

Assignment of grades (severity level) and attribution for each AE is to be completed at the site by the site Principal Investigator.

10.9 Routine AE Reporting Process

Routine reporting is defined as documentation and reporting of AEs on source documents and the AE case report form (CRF) for preparation of a report for DSMC review, quarterly reports to CDUS, and the final study report. All AEs **must** be reported in routine study data submissions per the I-SPY 2 TRIAL protocol and Manual of Operations and Procedures (MOP). **Routine study data submissions also are required when AEs are reported through the CTEP Adverse Event Reporting System (CTEP-AERS).**

Expedited reporting is defined as immediate notification of NCI and ACRIN per Section 10.8. Routine reporting requirements also apply as noted in the I-SPY 2 TRIAL protocol and MOP.

Appendix 2: Expedited Reporting Requirements for CIP Studies Using Commercial Imaging Agent(s) ONLY

For use in CIP studies involving commercial (non-IND/IDE) agents only

CIP Commercial Agent Studies: Expedited Reporting Requirements for Adverse events that Occur in a CIP Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Imaging Agent[1,2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- ~~"2~~4-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- ~~"1~~0 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 24 hours after the administration of gadolinium and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.10 Expedited Reporting to NCI and ACRIN

10.10.1 Expedited AE Reporting Timeline Definitions

- —24-hours; 5 calendar days"—The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event, followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
- —10-calendar days" — A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

10.10.2 24-Hour Telephone Reporting Instructions

Any AE/SAEs that require 24-hour notification are reported as follows:

10.10.2.1 AEMD Help Desk at (301) 897-7497

10.10.2.2 CIP– SAE Reporting Line: (301) 897-7402

- The CIP-SAE reporting line is staffed Monday through Friday from 7:30am – 7:30pm ET (Eastern Time).
- AE/SAEs may be reported via voicemail during off hours.
- A TRI contact for AE/SAE reporting will return your call within 24 hours.

10.10.2.3 ACRIN–AE/SAE Reporting Line: (215) 717-2763

- The ACRIN–AE/SAE reporting line is monitored by the ACRIN AE Coordinator: Monday through Friday from 8:30am – 4:30pm ET.
- AE/SAEs may be reported via voicemail during off hours.
- The ACRIN AE Coordinator will return your call within 24 hours.

10.10.2.4 Essential Details for Initiating an AE/SAE Report

- Name of person reporting the AE/SAE and telephone number
- Institution name and institution number
- Protocol title and number
- Participant's case number and initials
- Site principal investigator name and telephone number
- Date and time of the AE/SAE
- Date and time you learned of the AE/SAE
- Brief description of the AE/SAE
- Site principal investigator's assignment of the grade of the AE
- Site principal investigator's assignment of the attribution of the AE (do not delay initial report if not available)

IMPORTANT: After the 24-hour contact to CIP and ACRIN-AE/SAE reporting lines, an electronic CTEP-AERS must be submitted per the protocol-specific requirements or the regulatory reporting timelines, if not specified in the protocol.

10.10.3 Completion of CTEP-AERS

All SAEs that occur within 24 hours of DW-MRI require the submission of an electronic CTEP-AERS report within five (5) calendar days of first knowledge of the event is required.

AEMD helpline is available for any questions via phone at (301) 897-7497, available 24 hours a day (recorder after hours from 4:30pm – 8:00am Eastern Time).

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

10.11 Reporting Serious Adverse Events to I-SPY 2 TRIAL and FNIH

In addition to reporting serious adverse events relating to ACRIN 6698 to ACRIN and NCI, the I-SPY 2 TRIAL organizations will report SAEs on the I-SPY 2 TRIAL SAE Report Form.

Contact the Data Coordinating Center (DCC) Safety Department, Dr. Linda Doody, by phone within 24 hours of knowledge of the event.

Linda A. Doody, PhD DABT
CCS Associates, Inc.
1923 Landings Drive
Mountain View, CA 94043
Phone: (650) 691-4400 ext. 107
Mobile: (408) 221-6017
FAX: (650) 691-4410 44
Email: ispy2safety@ccsainc.com

Include the following information when calling:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call-back phone number
- Affiliation/Institution conducting the study
- Protocol number, title of protocol
- Description of the SAE, including reason serious and attribution to drug(s)

The organizations will fax or email the written SAE Report Form within 48 hours of learning of the event using the paper SAE form. The written SAE Report Form will be emailed (ispy2safety@ccsainc.com) or faxed to:

DCC, Safety Department
CCS Associates
Fax: (650) 691-4410
Phone: (650) 691-4400

DCC will triage the reported information and inform the study Medical Monitor, below:

Gary J. Kelloff, MD
NIH, NCI, DCTD Cancer Imaging Program
Rm 6058 EPN
6130 Executive Blvd
Bethesda, MD 20852
Phone: 301-496-9531
Fax: 301-480-3507
kelloffg@mail.nih.gov

The Medical Monitor and safety/regulatory staff will determine which SAEs require expedited FDA submission as safety reports. SAEs and AEs will be communicated to the relevant drug manufacturer per their individual safety reporting requirements regarding timing, frequency, and format.

All investigational sites will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

Follow-up of SAE: Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the study-specific SAE Report Form in the appropriate format. Follow-up information should be sent to the DCC Safety Department as soon as available. Continuing or new SAEs reported post-surgery will be followed until resolved or up to 12 months post-surgery. These events will be collected in the study database.

10.12 Local IRB Reporting

10.12.1 Adverse Event Reporting and Local IRB

AEs not requiring expedited reporting are reported to the local IRB in an annual report and/or continuing review report. All expedited AE reports should be sent to your local IRB per the local IRB policies and procedures. Please refer to your local IRB‘s policies regarding AEs and safety reports.

10.12.2 Expedited Serious Adverse Event Reporting and Local IRB

All expedited SAE reports may need to be reported to your local IRB, depending on local IRB policies and procedures.

11. ETHICAL CONSIDERATIONS

This study is to be conducted according to International Conference of Harmonisation [ICH] guidelines, U.S. federal regulations, standards of Good Clinical Practice, and ECOG-ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or IRB for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided before implementation of the study.

The investigator will provide the institution‘s Federalwide Assurance (FWA) number, along with the IRB approval letter and copy of the IRB-approved ICF. The investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s) and copy(s) of annual renewal(s).

All potential participants invited to join this study will be given an IRB-approved, site-specific ICF describing the study and providing sufficient information for participants to make informed

decisions about their participation in this study. The ICF will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB-approved ICF before the participant is subjected to any study procedures. The approved ICF MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent. Any revisions to the ICF at any time during the trial will need to be submitted to the local IRB for approval.

12. CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN Conflict of Interest policies and applicable federal, state, and local laws and regulations.

13. PUBLICATION POLICY

Neither complete nor any part of the results of the study obtained under this protocol, nor any information provided to the investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of ECOG-ACRIN and Nola Hylton. Any investigator involved in this study is obligated to provide ECOG-ACRIN with complete test results and all clinical data obtained from the participants in this protocol. Investigators will follow the ACRIN Publication Policy (available online at www.acrin.org/PublicationsPolicy.aspx).

14. INSTITUTIONAL MONITORING AND AUDITS

FNIH or their designee, the lead clinical site (UCSF) or FDA may monitor and/or audit various aspects of the study. ECOG-ACRIN will collaborate with these organizations to ensure protocol and regulatory compliance, and participants' welfare and safety. ECOG-ACRIN will obtain any monitoring and/or audit reports from the various organizations to ensure compliance. ECOG-ACRIN will perform monitoring reviews and/or audit visits as indicated. Sites are required to be given access to the facilities, databases, supplies, and records to review and verify data pertinent to the study.

14.1 Audits

If audits are deemed required, the audits will be conducted per procedures established by the NCI. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially-prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ECOG-ACRIN. IRB procedures, approvals, and ICFs will also be reviewed at the time of the audit visit.

14.2 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ECOG-ACRIN.

Source documents must verify the eligibility criteria and data submitted on all CRFs. If an item is not mentioned (e.g., history and physical examination alluding to a condition, but no mention of a psychological condition), it will be assumed it is not present.

Research records for each case should contain copies of the source documents for the data collected and reported to ECOG-ACRIN. If data are abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. Every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol. This will prevent any discrepancies and the inability to verify the document and the data reported.

14.3 Case Report Forms

CRFs are the primary data collection instruments for the study. The paper CRFs are provided as tools to the sites; they are not mandated to be used on site. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank on paper CRFs because the procedure was not done or the question was not asked, ―N/D" must be noted. If the item is not applicable to the individual case, ―N/A" must be noted. All entries on paper CRFs must be printed legibly in black. In the event of any entry errors, corrections must be made by drawing a **single straight line** through the incorrect entry, writing **the initials of the person making the correction, recording the date** when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to ICH Good Clinical Practice Guidelines.

If the paper CRFs are to be used as source documentation at the time of data collection, then 1) a ―Note to File' should indicate that the CRF is the source document and 2) the paper CRF must be signed and dated by the person who filled out the form.

15. STATISTICAL CONSIDERATIONS

15.1 Study Design and Endpoints

The study design is outlined in the schema. Patients who remain on study following the screening phase will be assigned to one of two major arms based upon their Her2 status. Within the two major arms, patients will be randomized to one of several sub-arms testing either paclitaxel alone or paclitaxel in combination with an investigational new drug, selected on the basis of phase I safety data and preliminary evidence of efficacy in the Her2+ or Her2- population (regimen A). Following regimen A, all patients will continue standard chemotherapy with doxorubicin and cyclophosphamide (regimen B). MRI and tissue-based biomarkers will be measured at four time points: 1) baseline, 2) after 3 weeks of regimen A, 3) following completion of regimen A and 4) at the end of regimen B, prior to surgery. With the randomization and stratification of the master I-SPY 2 study, participants on the ACRIN 6698 study may come from any treatment arm.

The primary endpoint of this study is pathologic complete response, and a secondary endpoint is assessment of the test-retest reproducibility of DW-MRI ADC metric.

15.2 Specific Aims and Analysis Plans

For Aims 1 to 3, the change in tumor ADC will be calculated as the difference in tumor ADC values from the specific treatment time point (T2, T3, or T4) to the baseline (T1) whereas the change in tumor volume or peak SER will be calculated as the difference in the marker values from the specific treatment time point (T2, T3, or T4) to the baseline (T1). The outcome will be

defined as a binary variable indicating either a pathologic complete responder (pCR) or a non-responder.

15.2.1 Primary Aims

Aim 1: To determine if the change in tumor ADC value measured from each treatment time point to baseline is predictive of pathologic complete response.

The receiver operating characteristic (ROC) curve will be constructed for the difference in tumor ADC value measured from each treatment time point to baseline and corresponding area under the ROC curve (AUC) will be estimated.

15.2.2 Secondary Aims

Aim 2: To determine if the combined measurement of change in tumor ADC value, change in tumor volume and change in peak SER is predictive of pathologic complete response.

We will use a data splitting approach where 60% of randomly selected observations will be selected as the training data set, and the rest of observations as the test data set. First, we will fit a multivariate logistic regression model using the training data set. In the model, a binary variable for pCR will be treated as the outcome variable and three markers (change in tumor ADC, change in tumor volume, and change in peak SER) as predictors. Then, we will derive a linear function of the three markers where the weight of each marker will be its corresponding estimated logistic regression coefficient. We will then apply the obtained linear function from the training set to the test data set and calculate the linear scores of the three markers. The ROC curve for the derived linear score and its corresponding AUC will be estimated.

Similarly, we will estimate the AUC for the DCE MRI markers (changes in tumor volume and peak SER), and assess whether the AUC of the three combined markers yields a higher AUC than the AUC of the DCE-MRI markers alone.

Aim 3: To investigate the relative effectiveness of the individual measurements, change in tumor ADC value, change in tumor volume, and change in peak signal enhancement ratio (SER) for predicting pathologic complete response in experimental treatment arms.

The ROC curve and its corresponding AUC for each individual marker will be estimated and compared in each experimental treatment arms. The sample size for each arm may vary between 20 – 120 patients. The significant differences in the three AUCs will be tested by the Z statistics (Hanley & McNeil, 1983) with adjustment of correlation between the AUCs.

Aim 4: To assess the test-retest repeatability of ADC metrics applied to breast tumor.

The repeatability coefficient (RC) and its 95% confidence interval (CI) will be estimated for each ADC metric described in Section 9.1.

The repeatability coefficient (RC) will be estimated by 2.77 times within-subject standard deviation (wSD). The one-way ANOVA model will be fitted to obtain the within-subject means of squares (WMS) where wSD can be

calculated by the square root of the WMS. Next, the 95% confidence interval for RC (RCLL, RCUL) will be derived by making use of the chi-squared distribution for the WMS.

15.3 Sample Size/Accrual Rate

The planned sample size is 404 participants at twenty institutions, to be accrued over 2 years (April, 2012 to March, 2014). Accrual rate is approximately 17 participants per month.

Patients who enroll on the ACRIN 6698 study will be recruited and enrolled from the ongoing I-SPY 2 TRIAL study. I-SPY 2 opened in March 2010 and will continue to enroll patients over a period of 3-4 years at 20 sites. I-SPY 2 follows an adaptive Phase II design with patients enrolled on up to 5 experimental arms. It is not known a priori how many patients will be enrolled in each experimental arm; the number enrolled can vary between a minimum of 20 and a maximum of 120. The ACRIN 6698 sample size estimate is based on enrollment of 404 consecutive patients from any of the five experimental arms.

15.4 Power Consideration/Stratification Factor

The sample size projections are designed to achieve adequate power for analyzing the early treatment time point measurement under Primary Aim 1. The number of subjects will be chosen to ensure 90% power to test whether the change in tumor ADC value measured from baseline to the early treatment time point is predictive of pathologic complete response.

Specifically, the sample size is calculated to detect a difference of 0.15 between the AUC under the null hypothesis of 0.5 and an AUC under the alternative hypothesis of 0.65 using a one-sided Z-test at a significance level of 0.05. It is assumed that the number of pCR non-responders is approximately 2.7 times greater than the number of complete responders based on the ACRIN 6657 study. Then, a total of 160 patients are required (43 responders and 117 non-responders) as shown in the table below.

We assume 20% of the cases accrued do not provide usable data for the analysis, for example, having missing MRI scans out of four MRI scans per participant, and assume that there is a 45% loss rate due to patients who are screened but do not proceed to the treatment phase of I-SPY 2. Additionally, 10% drop out rate is expected. Therefore, we will enroll approximately 404 participants after accounting for the above three conditions.

Computations were carried out using PASS (Hinze J. [2008] PASS, NCSS, LLC, Kaysville, Utah).

Table 3: Estimated Sample Sizes with power of 90%, type I error rate 5%

Power	N (total)	N+	N-	AUC0	AUC1
0.90018	160	43	117	0.5	0.65
0.90545	90	24	66	0.5	0.7
0.91062	56	15	41	0.5	0.75

Power: probability of rejecting a false null hypothesis.
N+: sample size in the pCR positive (complete responders) group
N- : sample size in the pCR negative (no-complete responders) group
AUC0: actual area under the ROC curve under the null hypothesis.
AUC1: actual area under the ROC curve under the alternative hypothesis.

Secondary aim 2 will evaluate ADC in addition to DCE-MRI markers of tumor volume and peak SER. Based on the ACRIN 6657 study, the AUC for the DCE-MRI markers is expected to be at least 0.7. Out of 160 analyzable data, 64 patients selected for the test data set will be used to construct the AUCs for the combined markers. It is assumed that 17 subjects are responders and 47 subjects are non-responders; and the correlation between the two linear scores (linear score for the DCE-MRI markers vs. linear score for the three combined markers) is assumed to be 0.35 for the responders and 0.69 for the non-responders. Under the above assumptions, the sample size of 64 patients will achieve 60% power to detect a difference of 0.15 between the estimated AUC of 0.7 for DCE-MRI alone and an AUC of 0.85 for combined ADC and DCE markers, using a one-sided z-test at a significance level of 0.05.

For secondary endpoint for assessing test-retest reproducibility of ADC:

We calculate the sample size required to ensure that the upper bound 95% confidence interval of the RC (RCUL) remains below the pre-defined biologically significant change in ADC value of 0.3 (x10-3) mm2/sec given potential observed RCs (Barnhart, Barboriak et al. 2009).

Estimations are based on the following assumptions:

- Replication per subject: 2
- Minimum change in ADC metric value that is of interest: 0.3 ($x10^{-3}$) mm^2/sec
- Expected (potentially observed) RC: 0.19, 0.2, 0.21.

Table 4: Estimated Sample sizes for the test-retest assessment of ADC

Significant change	Expected RC	Sample size
0.3 ($x10^{-3}$) mm^2/sec	0.19	15
	0.2	17
	0.21	20

According to the Estimated Sample Sizes table , we expect 15-20 participants to estimate RC. Since we have two or three vendors for the ADC measurements and wish to estimate the RC from each vendor, a total sample of (maximum) 60 is estimated for this aim.

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APPENDIX I:
SUPPLEMENTAL MATERIALS AVAILABLE ONLINE
ACRIN 6698

Supplemental materials that support the conduct of the trial are available on the ACRIN Web site at the ACRIN 6698 Protocol web page (www.acrin.org/6698 protocol.aspx). Types of materials posted online include:

- Data forms;
- Imaging materials (Image Transmittal Worksheet, imaging parameter charts, image submission instructions, and scanning and image qualification instructions), available directly via www.acrin.org/6698imagingmaterials.aspx;
- Recruitment and education materials;
- Regulatory resources, available directly via **www.acrin.org/pdrc.aspx**;
- Participating site list.

For more information related to the trial, contact the ACRIN 6698 Contact Personnel link on the above-mentioned Web page for a list of protocol team members at ECOG-ACRIN Diagnostic Imaging Headquarters and their roles.