

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6702

**A MULTI-CENTER STUDY EVALUATING THE UTILITY OF DIFFUSION
WEIGHTED IMAGING FOR DETECTION AND DIAGNOSIS OF BREAST CANCER**

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

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LIST OF ABBREVIATIONS AND ACRONYMS

ACR	American College of Radiology
ACRIN	American College of Radiology Imaging Network
ADC	Apparent Diffusion Coefficient
AE	Adverse Event
AUC	Area Under the Curve
BC	Biostatistics Center
BDMC	Biostatistics and Data Management Center
BI-RADS	Breast Imaging Reporting and Data System
Bx	Biopsy
CD	Compact Disk
CDUS	Clinical Data Update System
CIP	Cancer Imaging Program
cm	Centimeter
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTEP-AERS	CTEP Adverse Event Reporting System
CTSU	Cancer Trials Support Unit
DCE-MRI	Dynamic Contrast Enhanced-Magnetic Resonance Imaging
DCIS	Ductal carcinoma <i>in situ</i>
DICOM	Digital Imaging and Communications in Medicine
DMC	Data Management Center
DSMC	Data and Safety Monitoring Committee
DVD	Digital Video Disk <i>or</i> Digital Versatile Disk
DW	Diffusion Weighted
DWI	Diffusion Weighted Imaging
EC	Ethics Committee
eCRF	Electronic Clinical Research Form
FDA	Food and Drug Administration
FWA	Federal Wide Assurance (number)
GQA	General Qualifying Application
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
IND	Investigational New Drug
IPC	(ACRIN) Institutional Participants Committee
IRB	Institutional Review Board
LCIS	Lobular Carcinoma <i>in situ</i>
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
NCI	National Cancer Institute
N/D	Not Done
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OPEN	Oncology Patient Enrollment Network

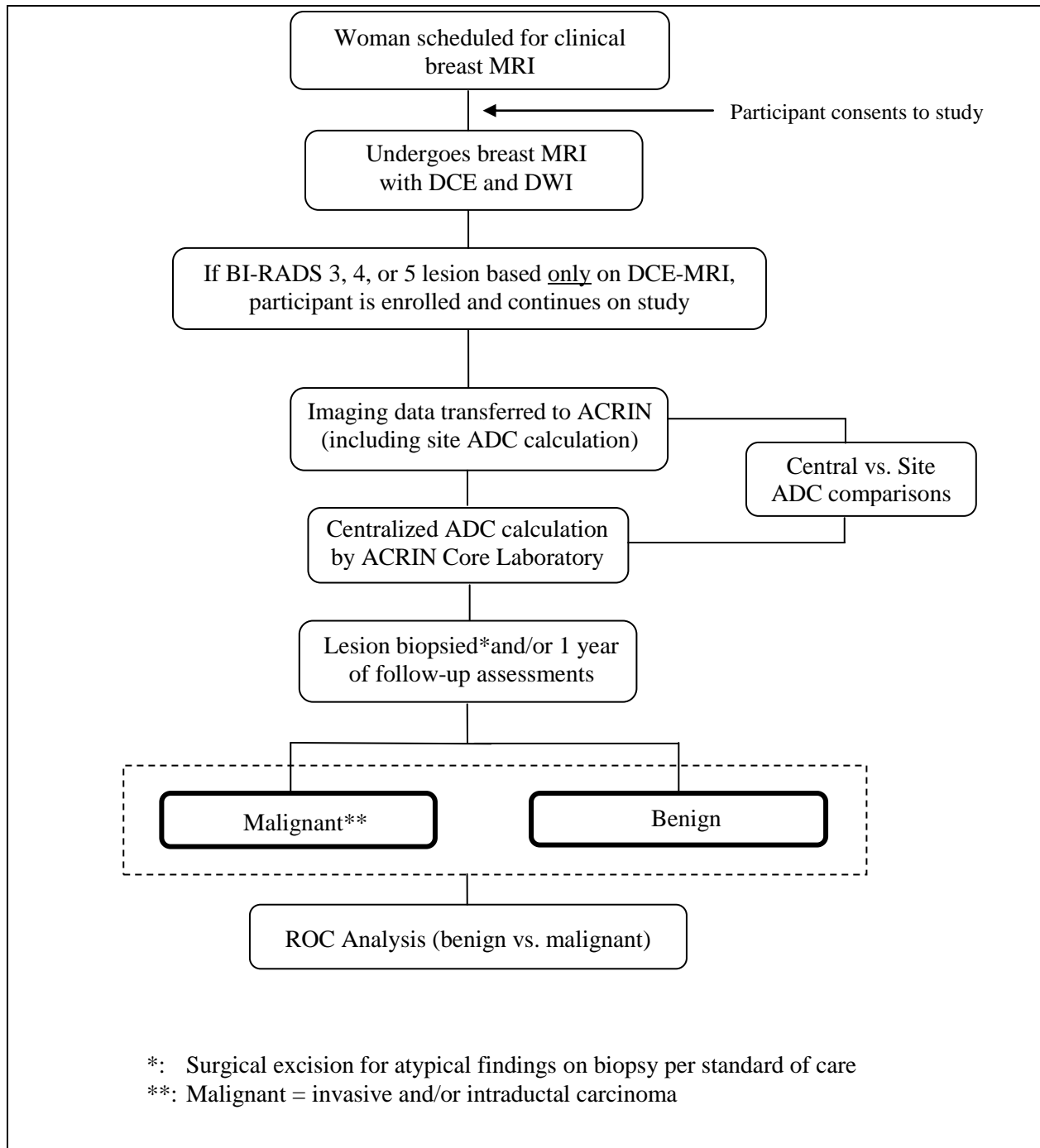
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PACS	Picture Archive and Communication System
PDRC	Protocol Development and Regulatory Compliance
PSA	Protocol Specific Application
PPV	Positive Predictive Value
QA	Quality Assurance
QC	Quality Control
RA	Research Associate
ROC	Receiver Operating Characteristic (Curve)
ROI	Region of Interest
RSS	Regulatory Support System
SAE	Serious Adverse Event
US	Ultrasound <i>or</i> United States

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6702: A MULTI-CENTER STUDY EVALUATING THE UTILITY OF
DIFFUSION WEIGHTED IMAGING FOR DETECTION AND DIAGNOSIS OF
BREAST CANCER

SCHEMA



STUDY OBJECTIVES/SPECIFIC AIMS

Primary objective:

To determine whether the Apparent Diffusion Coefficient (ADC), when used systematically in conjunction with conventional Dynamic Contrast Enhanced-Magnetic Resonance Imaging (DCE-MRI), can reduce the biopsy rate by at least 20% while maintaining sensitivity.

Secondary objective(s):

To determine whether optimal ADC cutoffs are different for mass and non-mass lesion types;

To determine whether site-generated ADC values differ significantly from those obtained by central review;

To determine whether the use of a nonzero minimum b-value to reduce perfusion effects in ADC calculation can increase the area under the curve (AUC) for differentiating benign and malignant lesions;

To determine whether the use of a normalized ADC measure (tumor/normal ratio) to account for inter- and intra-subject variations in water content and other factors can increase the AUC for differentiating benign and malignant lesions;

To determine whether ADC with nonzero minimum b-value and/or normalized ADC can reduce the biopsy rate while maintaining sensitivity.

ELIGIBILITY (*see Section 5.0 for details*)

Eligible participants are women 18 years or older who undergo a clinical breast MRI examination (including both DCE and DWI scans) by which a previously undiagnosed breast parenchymal lesion (BI-RADS 3, 4, or 5) is identified. Women undergoing high risk screening and local staging for a recently diagnosed breast cancer (in whom an additional lesion distinct from the known cancer is detected on MRI) may be the most common candidates, but others meeting the criteria will not be excluded. Outcomes (benign or malignant) will be determined for each study lesion by means of biopsy, surgical excision and/or follow-up assessments at 30 days, 6 months, and 12 months after the MRI. Participants receiving neoadjuvant chemotherapy within 6 months prior to MRI or between the MRI and determination of lesion outcome will be excluded.

SAMPLE SIZE

A total of 100 eligible participants with BI-RADS 3, 4, or 5 lesion(s) will be enrolled into this study at ACRIN-approved institutions that acquire DWI in their standard clinical MRI protocol. It is anticipated that approximately 8 - 10 participants per month will be accrued over 12 months. Total accrual at any given site will be limited to 40 participants.

1.0 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 American College of Radiology Imaging Network (ACRIN) research policies and procedures.

Magnetic resonance imaging (MRI) has become an important tool for breast imaging. Conventional breast MRI is highly sensitive for detecting cancer, but can also result in many false positives. Diffusion weighted imaging (DWI) can provide complementary information for lesion characterization by measuring the mobility of water molecules in tissue allowing an indirect assessment of tissue microstructure. Single center studies have shown promise for adding DWI to breast MR examinations to improve specificity; however, differences in study design have caused variable results and there is no consensus on the optimal approach. To determine the added value of DWI for reducing false positives of breast MRI, it is important to validate these findings in a multi-center study with DWI implemented across a variety of systems (manufacturers/models/magnet strengths). Furthermore, it is essential to use a standardized approach to breast DWI acquisition and analysis to identify optimal ADC thresholds for discriminating benign from malignant breast lesions.

For this study, we plan to evaluate DWI scans performed in women with breast lesions identified by conventional breast MRI. We will determine whether an ADC threshold can be defined for distinguishing benign and malignant lesions on DWI, assess the difference in ADC cutoffs for mass and non-mass lesions, and investigate the potential improvement in accuracy using techniques such as nonzero minimum b-value (to remove perfusion effects in the ADC measures) and normalized ADC measures (to account for variations in water content and other factors).

The outcomes of this study are potentially significant because if results are positive and DWI is found to be valuable for distinguishing benign from malignant breast lesions, (1) DWI could be easily implemented into routine clinical breast MR examinations (including screening exams) to improve specificity and reduce the number of unnecessary biopsies while adding only a few minutes to the exam and requiring no additional contrast or hardware, (2) the study will answer essential questions for implementing breast DWI in the multi-center clinical setting, such as establishing optimal ADC cutoff values and developing standardized image acquisition, data quality assurance, and interpretation methodologies, and (3) the study will provide valuable preliminary data and methodology to support a larger prospective Phase 3 trial to validate the improvement in diagnostic performance achieved by incorporating DWI into conventional breast MRI assessments. A negative result of the study will indicate that this technology is not yet ready for incorporating into standard breast MRI assessments and more work must be done to address specific issues identified by the study.

2.0 BACKGROUND AND SIGNIFICANCE

Conventional Breast MRI

Breast cancer is the second leading cause of cancer death among women in the United States, and earlier detection through screening is a fundamental way to improve survival. Dynamic contrast enhanced (DCE-MRI) of the breast has a high sensitivity for breast cancer detection and is the most sensitive technique for screening high-risk women (Kuhl, Weigel et al. 2010; Leach,

Boggis et al. 2005; Sardanelli, Podo et al. 2011) and detecting contralateral or multifocal disease in patients with recently diagnosed breast cancer (Lehman, Gatsonis et al. 2007).

However, overlap in the appearance of benign and malignant breast lesions on DCE-MRI can produce many false positives. In high-risk women, data from 9 studies have shown that MRI screening prompts a biopsy in approximately 7.8% of women, of which 40% are found to have cancer (MRI positive predictive value [PPV] = 40.3%) (Berg 2009). In women with newly diagnosed cancer, data from 16 studies have shown that MRI prompts biopsy for additional lesions in 16% of women, of which 66% are confirmed to be additional cancer (PPV=66%) (Houssami, Ciatto et al. 2008). Particularly in light of recent American Cancer Society guidelines recommending annual MRI screening for high risk women, estimated to affect up to 1.8 million women in the US, there is a clear and quickly growing need to improve the specificity of breast MRI in order to limit the number of unnecessary biopsies that will result from expanded use of this highly sensitive screening tool.

DWI of the Breast

Diffusion weighted imaging holds strong potential as an adjunct MRI technique for improving the specificity of conventional breast MRI. By measuring the mobility of water molecules in tissue, DWI indirectly assesses tissue microstructure and provides complementary information to DCE-MRI for lesion characterization. DWI is a short MRI sequence (< 5 minutes) that can be incorporated into a standard breast MRI protocol on clinical scanners. Numerous groups have demonstrated restricted water diffusion in breast malignancies and significant differences in ADC values of benign and malignant lesions. Further, recent single center studies report that ADC measures are complementary to DCE-MRI parameters for discriminating benign and malignant breast lesions and can increase the accuracy of conventional breast MRI assessment (El Khouli, Jacobs et al. 2010; Partridge, DeMartini et al. 2009; Partridge, Rahbar et al. 2011).

A study by Partridge et al. showed that in women with suspicious lesions detected on MRI, the application of an ADC threshold to determine who should undergo biopsy could prevent 33% of unnecessary biopsies without missing any cancers (Partridge, DeMartini et al. 2009). ADC was measured retrospectively in 83 suspicious lesions (31 malignant, 52 benign) that underwent biopsy based on conventional breast MRI assessment. The mean ADC for benign lesions was significantly higher than the mean ADC for malignancies, **Figure 1**. The PPV for DCE-MRI alone, calculated as the percent of lesions deemed suspicious and recommended for biopsy (classified BI-RADS 4 or 5) that were determined to be malignant, was 37%. Implementing an ADC cutoff ($ADC \leq 1.81 \times 10^{-3} \text{ mm}^2/\text{s}$) for biopsy recommendation improved the PPV from 37% to 47%, potentially sparing 17/52 (33%) women with suspicious lesions

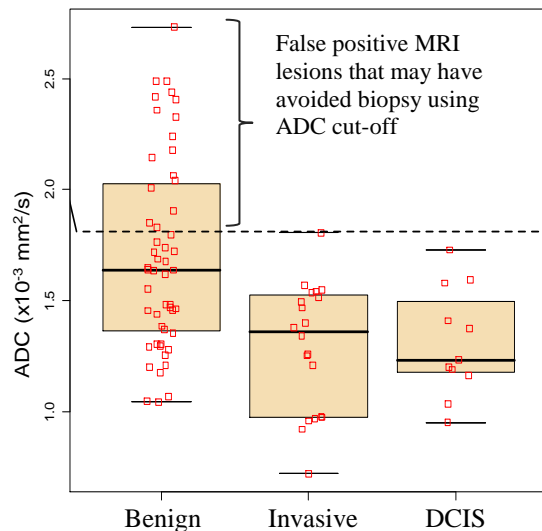


Figure 1. ADC values of suspicious lesions biopsied based on conventional breast MRI. Dotted line indicates the empirically-derived threshold ($ADC \leq 1.81 \times 10^{-3} \text{ mm}^2/\text{s}$) to provide optimal PPV with 100% sensitivity. From Partridge, DeMartini et al. 2009.

from unnecessary biopsies without missing any cancers.

El Khouli et al. assessed the incremental value of DWI and ADC mapping in relation to conventional breast MRI for characterization of benign versus malignant breast lesions (El Khouli, Jacobs et al. 2010). The study evaluated 101 lesions (68 malignant, 33 benign) in 93 women. Multivariate modeling was performed to predict malignancy based on morphologic features (margin, enhancement pattern) and DCE-MRI semi-quantitative kinetic curve data, along with DWI ADC measures. They found that normalized ADC measures improved the diagnostic performance of MR multivariate models to predict malignancy, particularly in premenopausal women. The area under the receiver operating characteristic (ROC) curve improved from 0.89 to 0.98, and the false-positive rate decreased from 36% (nine of 25 lesions) to 24% (six of 25 lesions), **Figure 2**.

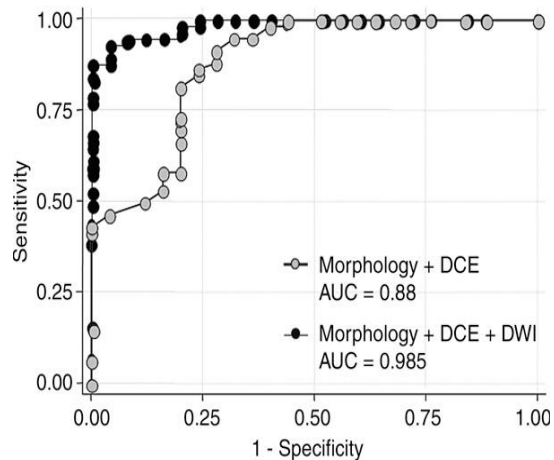


Figure 2. ROC curves for diagnostic models with and without normalized ADC measures from DWI. From El Khouli, Jacobs et al. 2010.

However, despite such promising findings from a variety of institutions, ADC measures have not been incorporated into clinical breast MRI interpretations or BI-RADS recommendations. Prior to widespread adoption of DWI for breast tumor assessment, well-controlled multi-center trials are required to validate the single center findings and define recommendations. There are a number of challenges in performing DW-MRI in a multi-center clinical trial setting, including issues surrounding lack of standardization in image acquisition and interpretation approaches, leading to variability in image quality and resulting diagnostic ADC criteria.

Rationale for Selected Approach

The techniques used to acquire DW images, including the choice of b-values, vary considerably across studies in the literature. There is also wide variation in image quality of breast DWI due to

the frequency of inadequate fat suppression and other imaging artifacts. Furthermore, DWI data analysis techniques vary widely including post-processing to include noise filtering, image registration, methods for region of interest (ROI) measurement (sub-region versus whole tumor characterization) and ADC calculation (tumor versus normalized). As a result, there are considerable differences in the reported ADC values of similar breast pathologies using different techniques.

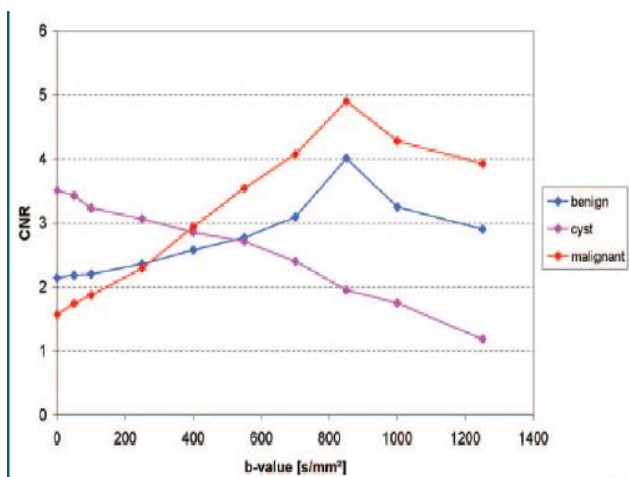


Figure 6: Mean CNR at DW imaging for benign and malignant lesions reached maximum at 850 sec/mm². Only CNR of cysts decreases constantly with increasing b values.

Figure 3. Influence of b-value on lesion Contrast to Noise (CNR), a measure of conspicuity. From Bogner, Gruber et al. 2009.

Bogner et al. assessed the effect of varying DWI b-values on conspicuity and ADC measures of benign (n=17) and malignant (n=24) breast lesions (Bogner, Gruber et al.

2009). They confirmed a linear dependence of lesion ADC measures on maximum b-value (over a range of $b=250$ to $1250 \text{ mm}^2/\text{s}$) and found optimal lesion conspicuity on DWI using a maximum b-value of $850 \text{ mm}^2/\text{s}$, **Figure 3**. They further showed that use of a nonzero minimum b-value (b_{\min}) for ADC calculations reduced perfusion effects in the ADC maps, **Figure 4**.

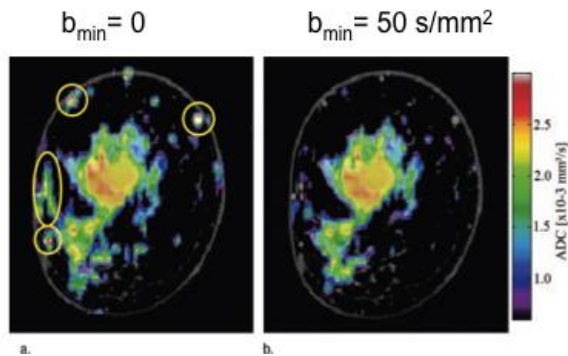


Figure 4. Nonzero b_{\min} reduces perfusion contributions from vessels on breast ADC maps. From Bogner, Gruber et al. 2009.

Our goal is to develop a standardized approach to breast DWI, identify optimal ADC thresholds for discriminating benign and malignant breast lesions, and investigate the potential of DWI for reducing false positives of breast MRI in a multi-center trial.

3.0 STUDY OBJECTIVES/SPECIFIC AIMS

3.1 Primary Aim

3.1.1 To determine whether the Apparent Diffusion Coefficient (ADC), when used systematically in conjunction with conventional DCE-MRI, can reduce the biopsy rate by at least 20% while maintaining sensitivity.

3.2 Secondary Aims

3.2.1 To determine whether optimal ADC cutoffs are different for mass and non-mass lesion types;

3.2.2 To determine whether site-generated ADC values differ significantly from those obtained by central review;

3.2.3 To determine whether the use of a nonzero minimum b-value to reduce perfusion effects in ADC calculation can increase the AUC for differentiating benign and malignant lesions;

3.2.4 To determine whether the use of a normalized ADC measure (tumor/normal ratio) to account for inter- and intra-subject variations in water content and other factors can increase the AUC for differentiating benign and malignant lesions;

3.2.5 To determine whether ADC with nonzero minimum b-value and/or normalized ADC can reduce the biopsy rate while maintaining sensitivity.

3.3 Primary Endpoint

Biopsy rate

3.4 Secondary Endpoints

False positive rate, area under the ROC curve, sensitivity, specificity, and positive predictive value.

4.0 STUDY OVERVIEW

This is a single arm multi-institution study with the primary objective of determining whether DWI can decrease the biopsy rate of conventional breast DCE-MRI. The study design incorporates observational analysis of DWI in women undergoing breast MRI. ADC values will be measured for breast lesions identified on DCE-MRI (BI-RADS 3, 4, or 5) to evaluate the ability to distinguish benign and malignant lesions based on ADC. We plan to recruit 100 women with breast lesions (BI-RADS 3, 4, or 5) identified by conventional breast DCE-MRI requiring

either biopsy, surgical excision or short-interval imaging follow-up. We anticipate accrual for the study will take 12 months, with approximately 10 participating ACRIN-approved sites that acquire DWI in their standard clinical MRI protocol. Total accrual at any given site will be limited to 40 participants. Site qualification for study participation will require passing quality control (QC) requirements as specified in Section 9.1. At participating sites, all potentially-eligible participants will be informed of the study and, if interested, will be consented prior to undergoing clinical breast MRI to include a DWI scan. Sites will use a standardized acquisition sequence per the study protocol. At the time of interpretation, the site radiologists will record a BI-RADS assessment to determine study eligibility prior to reviewing DWI. Those with lesions identified on MRI as BI-RADS 3, 4, or 5 will be enrolled in the study. Participants who do not have lesions assessed as BI-RADS 3, 4, or 5 will not be enrolled in the study. Sites will measure the lesion and normal-appearing breast tissue ADC values, and all images, measures, and associated clinical and pathological data will be sent to the ACRIN Core Laboratory. All enrolled participants will be followed at 30 days, 6 months, and 12 months post-MRI. ACRIN will perform a centralized read of DWI to measure lesion ADC and normal tissue ADC values, with researchers blinded to lesion outcomes and site ADC measurements. Data analysis will then be performed to compare ADC values in benign and malignant lesions and address the study objectives.

5.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

Eligible participants are women 18 years or older who undergo a clinical breast MR examination (including both DCE and DWI scans) by which a previously undiagnosed lesion (BI-RADS 3, 4, or 5) is identified. Women undergoing high risk screening and local staging for a recently diagnosed breast cancer (in whom an additional lesion distinct from the known cancer is detected on MRI) may be the most common candidates, but others meeting the criteria will not be excluded. Outcomes (benign or malignant) will be determined for each study lesion by means of biopsy, surgical excision and/or follow-up assessment at 30 days, 6 months and 12 months after the MRI.

5.1 Inclusion Criteria

- 5.1.1** Willing and able to provide written informed consent;
- 5.1.2** 18 years of age or older;
- 5.1.3** Successful completion of breast MR examination with DWI required by protocol;
- 5.1.4** Undiagnosed breast lesion (BI-RADS 3, 4, or 5) identified on MRI. The BI-RADS assessment must refer to a focal finding within the breast (i.e. mass, non-mass, or focus) as opposed to diffuse processes (e.g. background parenchymal enhancement, skin thickening) or lesions outside the subcutaneous breast (e.g. axillary lymph nodes, focal skin lesions, osseous lesions, etc.).

5.2 Exclusion Criteria

- 5.2.1** Participants with current or recent history (within 6 months prior to the MRI) of chemotherapy for cancer;
- 5.2.2** Neoadjuvant chemotherapy between MRI and confirmation of lesion outcome (study lesions must be biopsied prior to undergoing any chemotherapy);
- 5.2.3** Pregnant (if a female is of childbearing potential - defined as a pre-menopausal female capable of becoming pregnant - confirmation of pregnancy status per the site's standard of practice should be done prior to MRI);
- 5.2.4** Unwilling or not suitable to undergo MRI or use the contrast agent gadolinium.
Sites will comply with their institutional standard policies and procedures for

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performance and assessment of conducting MRI and the use of gadolinium in their patients.

5.3 Recruitment and Screening

The investigative team at each participating site will include a research coordinator, MR technician and/or physicist, and study radiologist. The research coordinator will be responsible for the identification and consent of participants. The radiologist will be responsible for ensuring that the interpretation of breast MRIs for eligible participants follows the study protocol (i.e. BI-RADS assessment for determining study eligibility must be performed and recorded prior to reviewing DWI).

Clinicians who manage breast health and breast cancer will refer potential participants by sending their patients for a clinical breast MRI for any indication. We anticipate these clinicians will include (but are not limited to) breast surgeons, breast oncologists, general practitioners (including internal medicine physicians, family medicine physicians, and nurse practitioners and physician assistants specializing in breast health), and radiation oncologists. There are no restrictions on the specialty or institutional affiliation for the clinician referring potential participants.

Patients at participating sites who are scheduled to undergo a clinical breast MRI examination including both DCE and DWI scans for any indication will constitute the potentially-eligible cohort and will be approached for participation in the study prior to undergoing breast MRI. For consented participants, radiologists will be required to first review only the conventional MR images (without DWI) to determine study eligibility. If an undiagnosed breast lesion is identified, the radiologist will record a BI-RADS assessment (ACR 2013 will be used for the duration of the study) and recommendation (biopsy or not) based on conventional images alone, prior to reviewing DWI, which will be used as primary outcome for the study. The decision to biopsy will be recorded before and after reading the DWI. Only participants with lesions deemed probably benign (BI-RADS 3) or malignant (BI-RADS 4 or 5) by conventional MRI will qualify for and will be enrolled in the study. Participants who do not have MRI-detected lesions assessed as BI-RADS 3, 4, or 5 are not eligible and will not be enrolled in the study. All enrolled participants will be followed at 30 days, 6 months, and 12 months post-MRI.

ACRIN will develop and provide recruitment materials for sites to use if they choose to do so. These handouts will be used by the research coordinator and site investigator(s) to aid in recruiting and consenting study participants. These handouts also will be disseminated to clinicians likely to refer patients for a clinical breast MRI. 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 US 2011 Census ethnic and racial demographics, and 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 below:

Gender and Minority Accrual Estimates

Ethnic Category	Females	Total
Hispanic or Latino	17	17
Not Hispanic or Latino	83	83
Ethnic Category: Total of all participants	100	100
Racial Category		
American Indian or Alaskan Native	2	2
Asian	5	5
Black or African American	14	14
Native Hawaiian or other Pacific Islander	1	1
White	78	78
Racial Category: Total of all participants	100	100

In order to target and recruit women from diverse ethnic communities, we will include sites from a range of geographic locations serving a variety of socioeconomic groups.

6.0 SITE SELECTION

6.1 Institution Requirements

The potential sites for this study are ACRIN-participating institutions that perform DWI as part of the clinical breast MRI protocol and meet qualifications for participating in this study. All sites must be either previously approved to participate in ACRIN clinical trials by having a General Qualifying Application (GQA) on file approved by the ACRIN Institutional Participants Committee (IPC), or submit a GQA for IPC review. In addition, each institution must submit 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 ACRIN 6702 protocol. The GQA and PSA can be found on the ACRIN web site at www.acrin.org/6702_protocol.aspx.

Sites also must obtain ACRIN DWI qualification for the scanner(s) that will be used for scanning trial participants. In addition, test images of the breast DWI 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/6702_imagingmaterials.aspx, and Section 9.0 provides detailed information regarding the DWI imaging protocol and related procedures.

6.2 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.

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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 sites 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 6702 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Pre-study requirements for patient enrollment on ACRIN 6702

- 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

6.3 Accrual Goals and Monitoring

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 100 participants with lesions assessed as BI-RADS 3, 4, or 5. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any recruitment barriers, including the ability to recruit minority populations. In particular, starting approximately one month after a site is approved to begin participant enrollment, the site's actual accrual will be compared to the average monthly accrual potential described in their PSA. Total accrual at any given site will be limited to 40 participants. When 50% of the study target accrual is reached (n = 50 participants), the accrual pattern will be evaluated to determine if any adjustments are necessary.

The ACRIN Steering Committee 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 ACRIN Data and Safety Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the DSMC may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating sites.

7.0 DATA MANAGEMENT/ONLINE REGISTRATION

7.1 General

- 7.1.1** Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at ACRIN in Philadelphia, PA.

- 7.1.2 Participant registration and data entry are available to clinical sites 24 hours a day, seven days a week. Participant registration occurs through Oncology Patient Enrollment Network (OPEN) and data collection through Medidata Rave.

7.2 Clinical Data Submission

- 7.2.1 **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.

Upon participant registration to the trial through OPEN via <https://OPEN.ctsu.org>, an electronic copy of the registration /eligibility data will be available in Medidata Rave.

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 ctscontact@westat.com.

- 7.2.2 **Data Collection/Medidata Rave:** Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS. To access iMedidata/Rave the site user must have an active CTEP IAM account (<https://eapps-ctep.nci.nih.gov/iam>).

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (<https://login.imedidata.com/selectlogin>) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/.

7.2.3 Please refer to the Forms Completion Guidelines for the forms submission schedule. The investigative site is required to submit data according to protocol. The case is closed when all data have been received, reviewed, and no outstanding data query exists for the case.

7.2.4 If a temporary problem prevents access to the URL, all sites are notified of the event and estimated down time. The investigative site should wait until access is restored to submit data. The site Research Associate (RA) or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored, as well as instructions for sites to proceed in the interim.

7.3 Data Security

Access to the system will be controlled by a sequence of identification codes and passwords.

7.4 Electronic Data Management

7.4.1 The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. The program is frequently updated to incorporate exceptions to rules. Any errors found by the BC will be reported to the DMC for resolution. All BDMC communication with the participating sites is normally done through the DMC.

7.4.2 If reviews at DMC or BC detect additional problematic data, the DMC personnel assigned to the protocol will initiate a query for the site RA or investigator specifying the problem and requesting clarification.

7.5 Data Quality Assurance

7.5.1 A goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. The BC at Brown University will access the study database for monitoring data quality and for performing analyses. Quality Assurance (QA) reviews are repeated at random intervals or per protocol during the course of a

given study. Any discrepancies and other data quality issues will be referred to DMC for resolution. No changes to the data will be made at the BC.

7.5.2 If patterns are discovered in the data that appear to arise from causes specific to a site, the BDMC will apprise ACRIN Headquarters, including the ACRIN Protocol Development and Regulatory Compliance (PDRC) department, who will then work with the site until the problem has been resolved. If the BDMC and PDRC cannot find a resolution to the problem, it will be brought to the ACRIN QA Committee for further discussion and resolution.

7.5.3 In addition, the ACRIN QA Monitor will review initial and annual regulatory documents and any revised regulatory documents. This monitoring process ensures protocol and regulatory compliance, participant's welfare and safety, and provides resources to sites for clarification to the protocol and guidance in completion of the electronic Clinical Research Forms (eCRFs).

8.0 STUDY PROCEDURES

Sites will recruit potential participants scheduled for a clinical breast MRI examination including both DCE and DWI scans. These participants should be consented for potential participation in the trial. Only participants with lesions deemed probably benign (BI-RADS 3) or malignant (BI-RADS 4 or 5) by conventional MRI will qualify for the study. After the potential participant has been deemed eligible, confirmed by conventional MR images (without DWI), sites will register the participant to the trial in Medidata Rave. Participants who do not have MRI-detected lesions assessed as BI-RADS 3, 4, or 5 are not eligible and will not be registered. Sites will comply with their institution's IRB requirements in maintaining a screening log of consented potential participants. Total accrual at any given site will be limited to 40 participants.

Each site will maintain all documentation of the screening and eligibility assessments, as well as documentation for all clinical procedures, as related to the trial and study-related procedures for source verification.

8.1 Visit 1: Screening/Eligibility Assessment

Due to scheduling constraints, it may not be possible to complete all required procedures in one day. Sites are encouraged to complete the screening/eligibility procedures within 4 weeks \pm 3 days of signed informed consent.

8.1.1 Obtain a signed informed consent form;

8.1.2 Screening assessment to determine eligibility will comprise the following:

- Assess eligibility to undergo breast MRI per the site's standard of practice, which may include:
 - Determination of adequate renal function;
 - Confirmation of pregnancy status for women of childbearing potential.
- Obtain medical history including:
 - Physical examination;
 - Recent chemotherapy treatment history.

8.1.3 Completion of clinically indicated DCE-MRI with DWI sequences;

8.1.4 Final determination of study eligibility is based on DCE-MRI clinical assessment, i.e., participant continues on study only if a BI-RADS 3, 4, or 5 lesion is detected.

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Participants who do not have a BI-RADS 3, 4, or 5 lesion detected will not be enrolled in the study.

- 8.1.5 Assessment for, documentation of, and reporting of AEs identified as related to MRI and gadolinium will conform to institutional policies and procedures;
- 8.1.6 Register the eligible participant;
- 8.1.7 Proceed with clinically recommended management plan for enrolled participants:
 - 8.1.7.1 Biopsy of suspicious MR-detected lesion(s);
 - 8.1.7.2 Surgical excision of suspicious MR-detected lesion(s) or
 - 8.1.7.3 Short interval imaging follow-up.

8.2 Visit 2: 30 Day Follow-Up

Thirty (30) days (\pm 3 days) after the MRI examination, a follow-up will occur either by telephone contact with the participant (or authorized proxy if necessary), in-person interview or by medical record review to determine if a biopsy, surgical excision, or no action was taken with respect to their suspicious MR-detected lesion(s). The authorized proxy will be contacted if the participant is not available and will only be queried about the participant's status.

- 8.2.1 If a biopsy or surgical excision was performed, the site will collect and record the final histopathology assessment.
- 8.2.2 If a biopsy or surgical excision is scheduled but not yet performed, the site will collect and record the final histopathology assessment when available.

8.3 Visit 3: 6 Month Follow-Up

All participants will be followed at 6 months (\pm 4 weeks) after their MRI examination. Results of any breast procedures performed in the months since the study MRI will be collected from the participant (or authorized proxy if necessary) by telephone contact, in-person interview or by medical record review by the site research staff. The authorized proxy will be contacted if the participant is not available and will only be queried about the participant's status.

- 8.3.1 Record results of any interim imaging, final histopathology assessment or clinical follow-up.

8.4 Visit 4: 12 Month Follow-Up

All participants will be followed at 12 months (\pm 4 weeks) after their MRI examination to confirm lesion outcome. Results of any breast procedures performed in the months since the study MRI may be collected from the participant (or authorized proxy if necessary) by telephone contact, in-person interview or by medical record review by the site research staff. The authorized proxy will be contacted if the participant is not available and will only be queried about the participant's status.

- 8.4.1 Record results of any interim imaging, final histopathology assessment or clinical follow-up.

8.5 Study Procedures Table

Study Procedure	VISIT 1: Screening/ Eligibility	VISIT 2: 30 Day Follow-Up (± 3 days)	VISIT 3: 6 Month Follow-Up (± 4wks)	VISIT 4: 12 Month Follow-Up (± 4wks)
Informed Consent Form	X			
Screening/Eligibility Review	X			
Medical History	X			
MRI with DCE and DWI ¹	X			
Clinical MRI Assessment to Determine Final Eligibility: BI-RAD 3, 4, or 5	X			
ACRIN Participant Registration	X			
Collection of Histopathology Report(s) ²		X	X	X
Follow-Up of All Study-Identified BI-RAD 3, 4, or 5 Lesions		X	X	X
AE Assessment	X			

¹: DWI should be performed prior to contrast administration for clinical DCE-MRI and should be performed in the same examination.

²: When available.

9.0 IMAGING PROTOCOL

9.1 Imaging Requirements and Parameters

MRI Procedures: All participating sites will use a standardized DWI acquisition sequence. The sequence will incorporate multiple b-values and good spatial resolution while maintaining adequate fat suppression and signal-to-noise. DWI will be acquired prior to DCE-MRI using a diffusion-weighted spin-echo echo planar imaging sequence. All vendors (GE, Philips, Siemens) 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, and 800 s/mm². The specific sequence parameters are provided in the Imaging Manual posted at www.acrin.org/6702_imagingmaterials.aspx.

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. Both 1.5 and 3 tesla field strengths will be allowed in ACRIN 6702, and identical QC criteria will be applied.

Image Processing and Analysis: ADC measures (in units mm²/s) will be performed in BI-RADS 3, 4, and 5 breast lesions identified on DCE-MRI. Sites will perform lesion ADC measurements according to the ROI measurement procedures described below. ADC maps generated from DW images and screen capture images showing ROI placement will be submitted in addition to originally acquired data to ACRIN Headquarters following each MRI exam. A list of the data required for transmission to ACRIN for each study case is given in the Imaging Manual.

Lesion ADC measurement: ADC measures will be performed by ROI by the site radiologist. An ROI will be drawn over the largest solid tumor region on DWI, with tumor size and location determined from corresponding DCE-MRI images. Areas of necrotic, cystic, or adipose tissue will be avoided by referencing to T1- and T2-weighted images and ADC maps in defining the ROIs. An additional ROI will be placed in a region of normal-appearing fibroglandular tissue for comparison. A screen capture will be saved in each case to illustrate ROI placement for reporting.

Alternative lesion 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, Gruber et al. 2009; Padhani, Liu 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. Normalized ADC values, which have been shown to improve diagnostic ability (El Khouli, Jacobs et al. 2010), will also be calculated by dividing lesion ADC by that of normal parenchyma in the same patient.

Site Qualification and Quality Control: Sites enrolling in ACRIN 6702 will be required to perform phantom QC testing and submit two DWI cases from human participants acquired using the multi- b value sequence outlined in 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 ACRIN 6702 participants 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 6702 Site Imaging Manual.

Extracted data including DCE-MRI BI-RADS characteristics using standardized interpretive criteria (ACR 2013) lesion size, as well as results of histopathology (if available) and 1-year follow-up will be submitted for all study participants. MRI scans (including DCE-MRI and DWI) and site-generated ADC values will also be submitted for each study participant for comparison with central review. ADC values will then be re-calculated by a central site (University of Washington) with researchers blinded to lesion outcomes (benign, malignant), but not blinded to DCE-MRI findings.

9.2 Images Submission

For TRIAD Submission: TRIAD® is ACR's proprietary image exchange application that will be used as the sole method of data transfer to the ACR Clinical Research Center Core Laboratory for this trial. ACRIN will provide installation on one or several computers of choice within the institutional "firewall" and on the institutional network; internet access is required. The TRIAD application can then be configured as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software de-identifies, encrypts, and performs a lossless

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compression of the images before they are transferred to the ACRIN image archive in Philadelphia. Once equipment-readiness has been determined, imaging personnel from ACRIN will coordinate installation and training for the software.

For more information, contact: TRIAD-support@phila.acr.org or call 215-940-8820.

10.0 ADVERSE EVENTS REPORTING

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

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- 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 Study-Related Adverse Events

There are no experimental procedures in this trial. Institutions are required to comply with their policies and procedures in reporting any adverse events related to the clinical care procedures. Please refer to your local IRB's policies regarding local AE reporting requirements.

10.6.1 Expected Adverse Events Associated With Standard of Care Practice Procedures

Any AEs that is a result of standard of care practice / treatment will be reported and managed per the institution's policies and procedures.

10.6.2 Expected Adverse Events Associated with Loss of Privacy

Participants in this study may be at risk of losing privacy of their protected health information (PHI). In addition to information collected from study procedures, information in the participating sites' study records may include personal and medical information extracted from the participants' medical records. Access to this information will be restricted to the site investigators, their study personnel, regulatory review board, study sponsor representatives, federal regulatory agencies, including any other trial representatives. Data submitted to ACRIN will be anonymized and participants will be identified by a study number assigned at the time of enrollment.

In the event of a breach, there is very little risk of harm to the participant. However, the site investigators and research personnel will be responsible for reporting the breach of confidentiality to their local IRB and ACRIN protocol team immediately upon discovery of the breach. Please refer to your institution's policies and procedures or contact your research compliance officer.

10.7 Source Documentation of Adverse Events

At the time of the MRI, the investigator or investigator-designee must seek information on AEs through discussion with the participant and, as appropriate, by examination. All expected (Section 10.6) and unexpected AEs considered possibly, probably, or definitely related to MRI, and SAEs will be documented in the study participant's chart and AE CRFs, in addition to meeting all study-specific reporting requirements of ACRIN, National Cancer Institute's Cancer Imaging Program (NCI/CIP), and the local IRB (per local IRB policy).

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 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 the ACRIN headquarters at **(215) 717-2763** for assistance.

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.

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 of AEs on source documents and the AE case report form (CRF), and submission to ACRIN 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. **Routine study data submissions also are required when AEs are reported through the Adverse Event Expedited Reporting System (CTEP-AERS).**

Expedited reporting is defined as immediate notification of NCI and ACRIN per Section 10.8. Routine reporting requirements also apply.

Since this is a diagnostic study that does not involve any experimental forms of cancer therapy, AE reporting will be minimal. ACRIN will collect and report only those AEs considered possibly, probably, or definitely related to the trial with the severity level of grades 3, 4, 5 that occur during study participation and up to 30 days after the last study procedure. Local IRBs and/or sites may stipulate additional AEs reporting based upon their review of the protocol.

10.10 Expedited Reporting to NCI and ACRIN

10.10.1 Expedited AE Reporting Timeline Definitions

There are no experimental procedures in this study. There should be no serious AEs that would require expedited reporting. However, in the event, a serious AE considered possibly, probably, or definitely related to study participation and NOT caused by standard of care practice, please comply with the following timelines.

- “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.

Use the NCI protocol number and the protocol-specific participant ID assigned during trial registration on all reports.

10.10.2 Investigator or investigator-designee must use expedited AE reporting for **deaths** with attribution of possible, probable, or definite due to study participation, including up to 30 days after the last study procedure. Deaths should be reported by telephone to NCI/CIP and ACRIN within 24 hours of first knowledge of the event and followed by an expedited written report within ten (10) days. Routine reporting requirements also apply (these reports should be sent to ACRIN, NCI/CIP, and the local IRB, in addition to documentation in participant chart and AE CRF).

10.10.3 All life-threatening/disabling unexpected AEs (considered possibly, probably, or definitely related to study participation) occurring during study participation and up to 30 days after the last study procedure will be reported within ten (10) working days of first knowledge of the event. Routine reporting requirements also apply (these reports should be sent to ACRIN, NCI/CIP, and the local IRB, in addition to documentation in participant chart and AE CRF).

10.10.4 All hospitalizations (or prolongation of existing hospitalization) for AEs with the severity (intensity) level of CTCAE grade 3, 4, or 5 and attribution of possibly, probably, or definitely related to study participation must be reported within ten (10) working days of first knowledge of the event, in addition to documentation in participant chart and AE CRF.

10.10.5 All other SAEs with attribution of possibly, probably, or definitely related to study participation must be reported within ten (10) working days of first knowledge of the event, in addition to documentation in participant chart and AE CRF.

10.10.6 Significant new information and/or follow-up information (e.g., test results, autopsy, discharge summary) on any on-going SAEs should be promptly reported to ACRIN.

10.10.7 24-Hour Telephone Reporting Instructions

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

10.10.7.1 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.

10.10.7.2 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.

10.10.7.3 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.

10.10.8 Completion of CTEP-AERS

All SAEs with attribution with possibly, probably, or definitely due to study participation that occur within 24 hours of standard of care 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-

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establishment of internet connection. In addition, the CTEP-AERS report must be faxed to the following:

- ACRIN SAE Fax Number: **(215) 940-8819**;

ACRIN contact to confirm receipt of CTEP-AERS report:

ACRIN AE Coordinator: **(215) 574-3150 (ACR Front Desk; ask for ACRIN AE Coordinator)**

To make a telephone report to NCI, contact at **(301) 897-7497**, available 24 hours a day (recorder after hours from 4:30pm – 8:00am Eastern Time).

Once the ACRIN AE Coordinator is notified of an SAE via 24 hour telephone report, and/or the electronic CTEP-AERS report, and receives email notification of submission, the following individuals will be notified via email:

To ACRIN:

Attention: ACRIN AE Coordinator

RE: Adverse Event Report

ACRIN Protocol 6702

1818 Market Street

Suite 1600

Philadelphia, PA 19103

10.11 Local IRB Reporting

10.11.1 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.

10.11.2 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.

11.0 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 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 to ACRIN before implementation of the study.

The investigator will provide ACRIN with 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

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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 and to ACRIN PDRC for review and filing.

12.0 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.

13.0 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 ACRIN, Savannah Partridge, PhD and the ACRIN Publication Committee. Any investigator involved in this study is obligated to provide 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).

14.0 INSTITUTIONAL MONITORING AND AUDITS

The investigator will permit study-related monitoring and auditing inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN. The investigator will ensure the capability for inspection of all participating sites' study-related facilities (e.g. imaging centers, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits.

14.1 Monitoring

Monitoring ensures protocol and regulatory compliance, participant's welfare and safety, and provides resources to sites for clarification to the protocol and guidance in completion of the CRFs. Monitoring of the protocol is implemented after the activation of the trial, and once participants have been enrolled into the study at each site. Each site will be informed when the monitoring of the protocol is implemented. Monitoring instructions will be sent to the site prior to the implementation of monitoring to aid in preparation for the monitoring. The instructions will specify regulatory documents and participant case records scheduled to be monitored. The ACRIN QA Monitor will review CRFs and source documents at several different time points: after first few participants enrolled and during the conduct of the trial, including staff changes at the participating sites. The QA Monitor will review the initial, annual, and any revised regulatory documents during each monitoring phase. **Please refer to the study-specific monitoring guidelines for details. The study-specific monitoring guidelines supersede the protocol's monitoring description.**

14.2 Audits

All participating sites that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the

protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants reaches 30% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after a site has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating sites not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.

Subsequent audits will be scheduled per the outcome of the initial audit. The audits will be conducted per procedures established by the Cancer Imaging Program (CIP) of 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 ACRIN. IRB procedures, approvals, and ICFs will also be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org. **Please refer to the study-specific audit guidelines for details. The study-specific audit guidelines supersede the protocol's audit description.**

To help sites prepare for monitoring and audits and to assure that the investigator and the research staff maintain records appropriately, ACRIN Headquarters will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial.

14.3 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 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 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.

14.4 Case Report Forms

CRFs, both web-based and paper forms, 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. If sites do use ACRIN-supplied CRFs, then 1) make sure they are complete; 2) ensure medical records are copied even if data are extracted from the medical records; 3) and use "N/D" and "N/A" appropriately. 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

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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 ink on the paper CRFs. 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](#).

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be reviewed against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires must be available for review. Required study image interpretation data that are more detailed in information than the image and not typically documented in the standard radiology report may be documented on the CRF and are acceptable source documentation **if signed by the Investigator**. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date of the exam(s) from the medical record(s).

If 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. If data are directly entered into the electronic CRF, the confirmation sheet should be printed out, signed and dated by the person completing the electronic CRF, and filed as a source document. Any use of approved CRFs as source documentation require a signature and date on the CRF with a reference to the information source (participant questionnaire, CT, MR, etc.). Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a major protocol deficiency.

14.5 Institutional Review Board/Ethics Committee

Sites must obtain initial, full-board, local IRB approval to participate in ACRIN trials. Prior to participant registration, a copy of the IRB approval letter for the protocol and the ICF must be sent to ACRIN, along with a copy of the IRB-approved, site-specific ICF. Any study-related materials for participants must be IRB reviewed and approved prior to distribution; approval notifications and other IRB correspondence should be delivered to ACRIN PD_RC. Investigator will provide a copy(ies) of IRB approval letter(s) for any amendment(s), and copy(ies) of annual renewal(s). International sites may use an Ethics Committee instead of an IRB.

15.0 STATISTICAL CONSIDERATIONS

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APPENDIX I: SUPPLEMENTAL MATERIALS AVAILABLE ONLINE

ACRIN 6702

Supplemental materials that support the conduct of the trial are available on the ACRIN Web site at the ACRIN 6702 Protocol web page (www.acrin.org/6702_protocol.aspx). Types of materials posted online include:

- Application and protocol activation documents (General Qualifying and Protocol Specific Applications, Form FDA 1572, protocol activation checklist, etc.);
- 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/6702_imagingmaterials.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 6702 Contact Personnel link on the above-mentioned Web page for a list of protocol team members at ACRIN Headquarters and their roles.