AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK and QUANTITATIVE IMAGING BIOMARKERS ALLIANCE

ACRIN 6701

Repeatability Assessment of Quantitative DCE-MRI and DWI: A Multicenter Study of Functional Imaging Standardization in the Prostate

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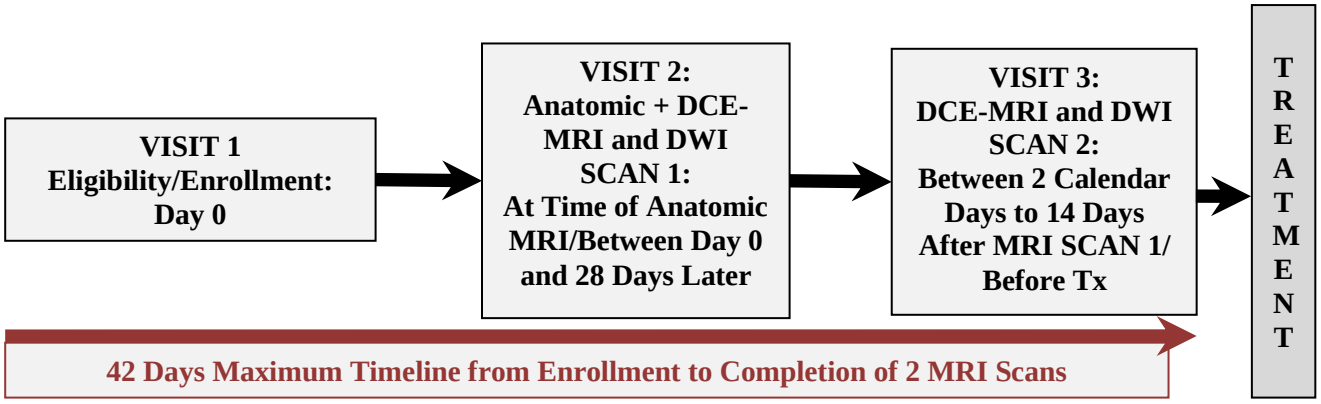
ACRIN 6701

Repeatability Assessment of Quantitative DCE-MRI and DWI: A Multicenter Study of Functional Imaging Standardization in the Prostate

SCHEMA



Definitions: DCE-MRI - dynamic contrast-enhanced magnetic resonance imaging; DWI - diffusion weighted imaging; Tx - treatment.

STUDY OBJECTIVES/SPECIFIC AIMS

The Quantitative Imaging Biomarkers Alliance (QIBA) dynamic contrast-enhanced-magnetic resonance imaging (DCE-MRI) committee is working to identify the limits of reproducibility of DCE-MRI quantitative metrics critical for useful biomarker studies. The ACRIN 6701 trial will examine the QIBA DCE-MRI profile claims regarding the repeatability of tumor DCE-MRI, as well as repeatability of diffusion weighted imaging (DWI) metrics, and evaluate the performance of these metrics in human subjects with prostate tumors. In addition to implementing the imaging protocol, the trial will introduce site imaging personnel to proper procedures for magnet qualification, the selection of tumor-bearing human subjects, and the implementation of the proper DCE-MRI and DWI parameters in general oncologic MRI.

Primary Hypothesis

Within the context of a multi-site clinical trial, the upper limits of the repeatability coefficient (RC) for DCE-MRI metrics K^{trans} and blood-normalized initial area under the gadolinium curve ($IAUCG90^{bn}$), and DWI metric D(t), using the whole prostate as a target lesion, can be demonstrated to be less than or equal to the pre-specified values that signify the minimal detectable significant biologic change of each quantitative MRI metric.

ELIGIBILITY *(see Section 5.0 for details)*

Men will be eligible for enrollment if they are ages 18 and older recently diagnosed with prostate cancer of greater-than minimal tumor burden (as defined in Section 5.0), planned for evaluation with MRI, willing to participate, and able to provide informed consent.

Exclusion Overview

- Not suitable to undergo MRI or receive gadolinium-based contrast agent (severe, untreatable claustrophobia; MRI-incompatible metallic objects or implanted medical devices; renal failure; weight greater than allowable by scanner per institutional standard practice);
- No anti-androgenic therapy within 30 days prior to enrollment;
- No prior external beam, proton, or brachytherapy to the prostate;
- No prior hip replacement or other major pelvic surgery.
- Unable or unwilling to provide consent to participate.

SAMPLE SIZE

Evaluable data from a total of 30 paired evaluable MRI examinations from eligible participants will be collected at a minimum of 6 participating institutions, representing each of the three major MRI vendors (Siemens, GE, and Philips). Stratification of participants will be equal across vendor platforms (i.e., 10 images from Siemens, 10 from GE, 10 from Philips).

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.

The ACRIN 6701 trial will assess the repeatability of the quantitative magnetic resonance imaging (MRI) assays dynamic contrast-enhanced (DCE-)MRI and diffusion weighted imaging (DWI). The primary goal of this study is to determine the repeatability of the main quantitative metrics (K^{trans} and blood-normalized initial area under the gadolinium curve [$IAUGC90^{bn}$] in DCE-MRI, and D[t] in DWI). The target population will be male patients undergoing MRI staging assessment for prostate cancer with 3T MRI. The prostate organ as a whole will act as the target "tumor" to gauge the repeatability coefficient of DCE-MRI and DWI, with the visible tumor nodule acting as a secondary target for analysis. The participants will serve as surrogates for the more general population of patients who undergo quantitative MRI analysis to gauge functional tumor responses to a variety of anti-cancer therapies. The results will guide radiologists, medical physicists, and oncologic scientists in defining standards of reproducibility when applying these technologies as imaging biomarkers in the course of early-phase clinical trials of traditional and novel anti-cancer therapies. While the results of this trial may not address all of the issues regarding the repeatability of DCE-MRI and DWI, such as technical variation in anatomic areas subject to respiratory motion, they are expected to provide important guidelines on the reproducibility of these quantitative imaging biomarkers in non-respiration-impacted structures. Furthermore, the importance of 3T imaging in oncologic MRI is emerging in many regions of the body (brain, breast, prostate, etc.), and the study will define limits of reproducibility of quantitative MRI at 3T.

2.0 BACKGROUND AND SIGNIFICANCE

The use of quantitative MRI biomarkers in cancer imaging has evolved substantially in the last decade. The advantages of MRI in clinical imaging—specifically the combination of high spatial resolution, exquisite intrinsic tissue contrast, and high sensitivity to extrinsic contrast agents—has made MRI an integral part of clinical oncologic imaging. In recent years, quantitative and semi-quantitative methods in MRI, particularly DCE-MRI and DWI, have become increasingly prevalent for detection of disease, characterization of focal lesions, and physiologic mapping of tumors in various regions of the body (Tofts, Brix et al. 1999; Thoeny, Ross. 2010). Both DCE-MRI and DWI have been proposed as methods for early determination of tumor response to traditional and targeted therapies (Leach, Brindle et al. 2005; Padhani, Koh et al. 2010). However, vendor-, software-, and institutional-specific differences in image acquisition protocols and methods of quantitative image analysis have hampered efforts to introduce these imaging techniques into large-scale clinical trials and/or general clinical practice. As such, the extraction of reliable and reproducible quantitative tumor metrics from MRI has been challenging. As these more functional MR techniques emerge as means of providing physiologic information about the tumor microenvironment, the imperative need is to define whether quantitative metrics can be reliably extracted from imaging currently performed in clinical practice, as well as how best to standardize imaging and post-processing/analytic techniques to provide reliable quantitative MRI metrics in oncologic imaging.

2.1 Goals of the RSNA Quantitative Imaging Biomarker Alliance (QIBA)

The Quantitative Imaging Biomarker Alliance (QIBA) group was formed in 2008 based on funding from the Radiologic Society of North America (RSNA) and, more recently, the National Institute of Biomedical Imaging and Bioengineering (NIBIB). Currently, three modality-based QIBA Committees exist: positron emission tomography (PET), computed tomography (CT), and MRI. The MRI Modality Committee is further subdivided into DCE-MRI and functional MRI (fMRI) technical committees. Most recently, the MRI Modality Committee has developed a proposal to be submitted to the QIBA Steering Committee to request the formation of a Diffusion MRI Technical Committee to address quantitative DWI biomarkers. The DCE-MRI committee has established two key areas of challenge in quantitative DCE-MRI: 1) sources of variability in measurement of longitudinal relaxation time (T_1) (Guo, Reddick et al. 2009), and 2) array coil bias field correction (Ashton, Raunig et al. 2008). The DCE-MRI subcommittee has established and tested a DCE-MRI phantom to assess MRI scanner performance in these areas. (Jackson, Gupta et al. *QIBA DCE-MRI Technical Committee Update: Phantom Series and First DCE-MRI Profile*. Panel discussion, RSNA 2010).

Ultimately, the goal of the QIBA DCE-MRI committee is to provide guidance to the imaging community for the most efficacious and reproducible methods of DCE-MR image acquisition and analysis, so as to further investigation of the use of DCE-MRI as a biomarker in oncologic imaging studies. Toward this end, a preliminary document, termed the DCE-MRI "profile" has been created by the QIBA DCE-MRI committee (QIBA DCE-MRI Profile v1.0. 2011), based on the organizational aspects of imaging guidance documents proposed by Buckler et al (Buckler, Mozley et al. 2010; Buckler, Bresolin et al. 2011). The combined investigation of perfusion and diffusion in DCE-MRI and DWI acquisitions is in alignment with newer developments in investigating angiogenesis and tumor microenvironment by MRI and reflects the strategic approach of the QIBA DCE-MRI committee.

2.2 DCE-MRI in Quantification of Tumor Vascularity

DCE-MRI has evolved as a method of quantifying the vascularity of tumors and other tissues In DCE-MRI studies, the changes in tissue image intensity over time are measured through high-frame rate repeated T1-weighted (T1W) imaging before and during gadolinium administration. While multi-phase enhanced MR imaging has been used in a variety of clinical MRI studies (Kuhl, Mielcareck et al. 1999; Schnall, Blume et al. 2006; Hamm, Mahfouz et al. 1997; Low, Francis et al. 1993), quantitative and semi-quantitative approaches to dynamic enhanced diagnostic MRI of the body are a more recent phenomenon (Notohamiprodjo, Sourbron et al. 2010; Coenegrachts, Van Steenbergen et al. 2004).

Due to the arbitrary scaling of tissue signal intensity in MRI, successful use of DCE-MRI to evaluate tumor vascular characteristics in the clinic requires a method to translate the kinetic enhancement features observed during DCE-MRI into one or more quantitative metrics. The two metrics most frequently utilized by investigators are the first-order transfer rate of gadolinium from plasma to tissue, indicated as K^{trans} (Tofts, Brix et al. 1999), and the initial area under the gadolinium time curve, or IAUGC (Evelhoch 1999), the latter often normalized to the arterial blood gadolinium function, or $IAUGC^{bn}$ (Ashton, Raunig et al. 2008). As a metric directly related to defining physiologic parameters (i.e. blood flow vessel and permeability), K^{trans} has emerged as the quantitative imaging metric of choice in human studies. While IAUGC has also been used successfully in DCE-MRI studies, this metric does not have a direct correlate to the physiologic attributes of the tumor neo-vascular micro-environment that is reflected in the metric K^{trans}.

DCE-MRI has been used successfully as a means of assessing the vascular effects of anti-angiogenic and anti-vascular agents in a large number of phase I and phase II human clinical trials (Dowlati, Robertson et al. 2002; Mross, Fuxius et al. 2002; Galbraith, Maxwell et al. 2003; Morgan, Thomas et al. 2003; Stevenson, Rosen et al. 2003; Medved, Karczmar et al. 2004; Flaherty, Rosen et al. 2008; Sorensen, Batchelor et al. 2009; Wong, Koh et al. 2009). For example, early trials showed proof of principle in anti-vascular activity of anti-angiogenic agents with significantly reduced blood flow visible by DCE-MRI in phase I trials of these novel agents (Dowlati, Robertson et al. 2002; Galbraith, Maxwell et al. 2003; Morgan, Thomas et al. 2003; Stevenson, Rosen et al. 2003). As the technology and pharmacodynamics of anti-angiogenic therapies have advanced in the past decade, interest in the application of DCE-MRI to relate vascular effect to outcome has increased, especially in highly-angiogenic tumors such as glioblastomas and renal cell carcinoma (Flaherty, Rosen et al. 2008; Sorensen, Batchelor et al. 2009).

2.3 Reproducibility of DCE-MRI in Human Studies

Despite the success of DCE-MRI as a potential biomarker in assessing tumor response to vascularly-targeted agents, the reproducibility of DCE-MRI metrics, including K^{trans}, has remained a concern. A number of assumptions are made to model the expected behavior of MRI signal intensity after gadolinium introduction. Errors in estimates of key input parameters, including the baseline tumor T1 value or the true nature of the arterial input function (AIF) can affect results dramatically (Guo, Reddick et al. 2009).

Early studies of DCE-MRI repeatability demonstrated relatively large coefficients of variation (Lankester, Taylor et al. 2005). More recent studies have demonstrated that improved reproducibility is possible with attention to modeling and careful measurement of patient AIF (Ashton, Raunig et al. 2008; Mendichovsky, Cutajar et al. 2009; Ng, Raunig et al. 2010). Nevertheless, relatively few studies of DCE-MRI reproducibility in a multi-site setting have been performed.

2.4 DWI in Cancer

DWI measures the random or Brownian motion of tissue water molecules via the use of spatial gradients applied during the acquisition of rapid echo-planar sequences. DWI was first introduced successfully as a means of detecting abnormal water mobility in areas of acute ischemic stroke in the brain (Le Bihan, Turner et al. 1992). DWI was then applied to evaluating the mobility of water in brain tumors (Le Bihan, Douek et al. 1993). More recently, diffusion applications have found use throughout the body as a means of detecting abnormal water motion restriction in tumors outside of the central nervous system (Koh and Collins. 2007; Chandarana and Taouli. 2010).

Quantitative evaluation of DWI relies on the calculation of the apparent diffusion coefficient, or ADC, of tumors. Quantitative DWI analysis has demonstrated that biologic aspects of different tumors can be graded based on their diffusion characteristics (Nasu, Kuroki et al. 2009; Costantini, Belli et al. 2010; Hambrock, Somford et al. 2011). Serial quantitative DWI have also been utilized to demonstrate early changes in tumor microenvironment following initiation of chemotherapy (Li, Cheng et al. 2011; Wu, Kellokumpu-Lehtinen et al. 2011; Zhang, Chen et al. 2011). The need for expansion of the use of DWI in cancer imaging was recently highlighted (Padhani, Liu et al. 2009).

While the apparent diffusion coefficient (ADC) is the metric primarily described in quantitative imaging analysis, in multiple B-value DWI studies, a biexponential behavior of the signal intensity (SI) changes during application of diffusion gradients is noted (Le Bihan, Breton et al. 1986). This effect is most

attributed to a population of protons that undergo more rapid signal loss at weaker diffusion gradient strengths due to intra-voxel motion dominated by tissue perfusion. A larger fraction of the protons then undergo more modest diffusion-gradient induced decline in SI due to Brownian motion from true water diffusion. Efforts to reliably measure the rapid ("perfusional") diffusion component (referred to as pseudo-diffusion, D*, of D[p]) in tumors requires a large number of B values, and have had variable success. However, it has been suggested that elimination of the perfusional component of diffusion in the prostate can be achieved when only b values greater than 100 s/mm^2 are used (Riches, Hawtin et al. 2009).

2.5 Reproducibility of Quantitative DWI in Human Studies

Given the ease of DWI acquisition (short acquisition times, lack of contrast administration), it has been easier to obtain estimates of ADC reproducibility in human studies. Estimates of the reproducibility of DWI in non-central nervous system human tissues suggest that ADC estimate accuracy ranges from 15% to 30% (Gibbs, Pickles et al. 2007; Kim, Lee et al. 2010; Rosenkrantz, Oei et al. 2011). However, multi B-value diffusion imaging, which may provide information regarding both the true diffusion of water (D[t]) and the intravoxel incoherent motion, attributed to perfusional motion of blood within tissues (D[p]), is being increasingly investigated as a means of expanding the range of imaging biomarkers available within the diffusion MRI examination (Chandarana, Lee et al. 2011; Klauss, Lemke et al. 2011; Sigmund, Cho et al. 2011).

2.6 DCE-MRI and DWI in Prostate Imaging

While many quantitative MRI investigations in tumor imaging, especially DCE-MRI, have focused on tumor therapeutic response assessment, there is an emerging body of data on the use of both methods in diagnostic prostate imaging. DWI, especially, has been shown to be a promising adjunctive imaging technique to traditional T2-weighted (T2W) MR imaging for detection of prostate cancer (Turkbey, Pinto et al. 2010). Quantitative DWI analysis has demonstrated strong correlation between tumor ADC and Gleason score (Hambrock, Somford et al. 2011), a result suggesting the potential of DWI to supplement sextant biopsy to map the presence and degree of "aggressive" (e.g. Gleason score 7 or greater) tumor. DCE-MRI has also been used to successfully identify prostate cancer as an adjunct to morphologic imaging (Somford, Futterer et al. 2008), and degree of tumor vascularity strongly correlates with microvessel density and other markers of tumor angiogenesis (Ren, Huan et al. 2008).

2.7 Rationale for Study Population and Imaging Plan

2.7.1 Rationale for the Current Patient Population for Repeatability Testing

The choice of a study cohort comprising patients with prostate cancer undergoing clinical staging by MRI highlights a consensus agreement of the study chair and members of the QIBA DCE-MRI committee that this patient group represents a viable target population for a test-retest study easily accessible to study teams at a large number of tertiary case imaging centers. More specifically, this population provides an appropriate target "tumor" (i.e., the prostate itself) in the "torso" region of the body while limiting the effects of physiologic motion; provides for similar anatomic prescription among all patients; and presents a patient population that includes individuals easily accessible to participating sites based on current clinical practices. While respiratory motion is common in tumors located in many metastatic locations (e.g. lower lungs and liver), tumors in other anatomic areas (including the retroperitoneum, pelvis, bones, and lung

apices) do not undergo severe respiratory motion. The prostate therefore represents an excellent surrogate for malignant tumors in these anatomic locations.

2.7.2 Rationale for Use of 3T Field Strength

In order to increase the technical homogeneity of this study, ACRIN 6701 limits acquisition to 3T MRI scanner systems. As 3T MRI is fast becoming the magnet strength of choice for prostate evaluation in academic imaging centers, limiting the study to 3T imaging reduces the number of variables that may confound analysis of global and vendor/institution-specific quantitative imaging repeatability. Depending on local practices of participating sites, the use of 3T may reduce the need for endorectal coil anatomic (i.e., T2W) imaging, facilitating participant throughput during the imaging sessions. It is recognized that much of the quantitative oncologic imaging research outside of the brain is currently performed at 1.5T, and that higher variation in field homogeneity at 3T may increase errors in quantitative MRI (Azlan, Di Giovanni. 2010). However, in other aspects, estimates of quantitative MR imaging reproducibility at 3T are currently felt to be similar to that at 1.5T (Garrett, Agrawal et al. 2009**)**. As such, estimates for the minimal change in tumor DCE-MRI and DWI metrics that can be attributed to treatment effect based on repeatability coefficients achieved in this study at 3T may be safely transferred to protocols performed at 1.5T, with confidence that the repeatability coefficient (RC) of the quantitative imaging metric on a 1.5T MRI system will be similar, if not smaller, than that demonstrated at 3T.

2.8 The ACRIN 6701 Trial Examines the QIBA DCE-MRI Profile and DWI Reproducibility

In order to substantiate the QIBA DCE-MRI profile claims regarding the repeatability of tumor DCE-MRI metrics, it is necessary to evaluate the performance of the QIBA DCE-MRI profile in human subjects with tumors. This process would include not only implementing the imaging protocol, but also introducing site imaging personnel to proper procedures for magnet qualification, the selection of tumor-bearing human subjects, and the implementation of the proper DCE-MRI imaging exam to these subjects. To this end, the QIBA DCE-MRI committee has agreed to partner with ACRIN to facilitate the development and implementation of the test-retest DCE-MRI human study. The ACRIN 6701 trial will test the claims of the QIBA DCE-MRI profile and aid in identifying the limits of reproducibility of quantitative MRI metrics, especially in the multi-site setting critical to useful biomarker studies.

The target population, patients presenting for MRI of the prostate to stage newly-diagnoses tumor, will be approached for participation in this study. Participants will undergo two successive quantitative MRI examinations, performed before therapy within a distinct time frame. Results from this study will gauge the repeatability of image-based extraction of quantitative metrics from DCE-MRI and DWI.

2.9 Study Hypotheses

- Hypothesis #1: The repeatability coefficient (RC) of the DCE-MRI metric K^{trans}, as measured by median pixel values of the whole prostate, is equal to or less than 22%.

- Hypothesis #2: The RC of the DCE-MRI metric $IAUGC90^{bn}$ (blood-normalized initial area under the gadolinium curve between 0 and 90 seconds), as measured by median pixel values of the whole prostate, is equal to or less than 0.05 (in normalized units).

- Hypothesis #3: The RC of DWI metric D(t), as measured by median pixel values of the whole prostate, is equal to or less than 0.3 x 10^{-3} mm^2/sec.

3.0 STUDY OBJECTIVES/SPECIFIC AIMS

3.1 Primary Aims

3.1.1 Determine the test-retest performance, assessed by the repeatability coefficient [RC] of K^{trans} and $IAUGC90^{bn}$ and measured by median pixel values of the whole prostate.

3.1.2 Determine the test-retest performance, assessed by the RC of D(t) and measured by median pixel values of the whole prostate.

3.2 Secondary Aims

3.2.1 DCE-MRI Methodology Secondary Objectives

3.2.1.1 Determine the test-retest performance, assessed by RC of K^{trans}, $IAUGC90^{bn}$, and D(t), and measured by median pixel values of the dominant prostate tumor.

3.2.1.2 Determine the effect of reader on the RC of DCE-MRI and DWI metrics for whole prostate and tumor nodule target lesion.

3.2.1.3 Determine whether T1-dependent or T1-independent methods for gadolinium quantification in DCE-MRI studies produce differing values for the RC for K^{trans} and $IAUGC90^{bn}$.

3.3 Exploratory Aim

3.3.1 Explore the correlation between DCE-MRI and DWI metrics for both whole prostate and dominant tumor nodule as target lesions.

4.0 STUDY OVERVIEW

ACRIN 6701 QIBA is a test-retest assessment of quantitative MR measurements of whole prostate and prostate tumor lesions on DCE-MRI and DWI scans. Participants will comprise males 18 years and older with recent diagnosis of adenocarcinoma of the prostate who meet minimum tumor burden parameters and other eligibility criteria as defined in Section 5.0 of the protocol. Evaluable images and data will be collected from 30 eligible trial participants during an approximately two-year recruitment timeline, followed by assessment in a central reader study for the primary aim. Enrollment must take place between 28 and 90 days after prostate cancer diagnosis by transrectal ultrasound biopsy (TRUS). MRI SCAN 1 should be scheduled between 0 and 28 days after enrollment, and MRI SCAN 2 will be performed no earlier than 2 calendar days and no later than 14 days after completion of MRI SCAN 1. Both MRI studies must be completed prior to treatment of the prostate cancer.

Adverse events reported from events occurring within 24 hours after each of the study-related imaging scans should be reported according to Section 10.0. General trial procedures are outlined in Section 8.0 of the protocol; specifics on the imaging procedures are available in Section 9.0; and imaging parameters by vendor are available in the ACRIN 6701 Imaging Manual at www.acrin.org/6701_protocol.aspx. Any images found on central quality control assessment to be either inevaluable or to belong to patients with too-low tumor burden will need to be replaced with images from newly-recruited participants (see Section 8.4 for off-study criteria and participant-replacement details).

5.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

5.1.1 Men 18 years of age or older;

5.1.2 Diagnosis of prostate cancer by transrectal ultrasound (TRUS)-guided biopsy between 28 to 90 days prior to enrollment;

5.1.3 Minimal tumor burden as defined by at least one of the following criteria:

i. One single core with ≥ 50% cancer burden and ≥ 5 mm tumor length;

ii. Two or more cores in the same prostate region, each with ≥ 30% cancer burden;

iii. Three or more cores positive for prostate cancer (of any magnitude of cancer burden) in the same prostate region;

iv. Gleason score of 7 or higher cancer burden;

v. PSA ≥ 10 ng/mL;

5.1.4 Able to tolerate MR imaging required by protocol, to be performed at an ACRIN-qualified facility and scanner;

5.1.5 Willing and able to provide a written informed consent.

5.2 Exclusion Criteria

5.2.1 Not suitable to undergo MRI or use the contrast agent gadolinium-based contrast agent because of:

5.2.1.1 Severe claustrophobia not relieved by oral anxiolytics per institutional standard practice;

5.2.1.2 Presence of MRI-incompatible metallic objects or implanted medical devices in body (including but not limited to: non-MRI compatible metal objects, cardiac pacemaker, aneurysm clips, artificial heart valves with steel parts, metal fragments in the eye or central nervous system);

5.2.1.3 Renal failure, as determined by glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 based on a serum creatinine level obtained within 48 hours prior to enrollment;

5.2.1.4 Weight greater than that allowable by the MRI table, per local institutional practice;

5.2.2 Anti-androgenic therapy within 30 days prior to enrollment;

5.2.3 Prior external beam, proton, or brachytherapy to the prostate;

5.2.4 Prior hip replacement or other major pelvic surgery.

5.3 Recruitment and Screening

The investigative team at each participating site includes the referring clinician (urologist or radiation oncologist), radiologist, and trial personnel responsible for recruiting and data integrity. Potential participants will be referred via outpatient radiology/MRI clinics schedules, as well as from participating urology and radiation oncology clinics.

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

ACRIN 6701 trial is a prostate and prostate cancer study, Women are excluded for the study. Eligible men from all ethnic groups will be enrolled into this trial.

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	Sex/Gender		
	Females	**Males**	**Total**
Hispanic or Latino	N/A	4	4
Not Hispanic or Latino	N/A	26	26
Ethnic Category: Total of all subjects	N/A	**30**	**30**
Racial Category			
American Indian or Alaskan Native	N/A	1	1
Asian	N/A	2	2
Black or African American	N/A	5	5
Native Hawaiian or other Pacific Islander	N/A	1	1
White	N/A	21	21
Racial Category: Total of all subjects	N/A	**30**	**30**

6.0 SITE SELECTION

6.1 Institution Requirements

The potential sites for this study are ACRIN-participating institutions that 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 6701 protocol. The GQA and PSA can be found on the ACRIN web site at www.acrin.org/6701_protocol.aspx.

Sites need to have a proven record of 50 prostate MRI examinations per year. A 3T MRI scanner with hardware and software that meet protocol requirements for DCE-MRI and DWI must be available for clinical research at the sites. The site research team will comprise the site PI radiologist, MRI

technologist(s), referring clinicians(s), and clinical research staff of coordinators, nurses, patient advocates, etc. Sites will indicate a lead study radiologist with expertise in prostate MRI. Sites will also indicate the 3T MRI scanner vendor and model to be used throughout the study. It is strongly recommended that all trial imaging be performed on a single scanner system.

Sites also must obtain ACRIN 6701 qualification for the scanner(s) that will be used for scanning trial participants. In addition, images of the DCE-MRI and DWI phantom scans per protocol specifications must be reviewed and approved by the ACRIN Core Laboratory. Feedback from initial participants' images submissions will be provided from the ACRIN Core Lab for quality control purposes. All scanner and image qualification materials are available in the ACRIN 6701 Imaging Manual available at www.acrin.org/6701_imagingmaterials.aspx. Section 9.0 provides an overview of the DCE-MRI and DWI imaging procedures, including distinctions in procedures with and without use of the endorectal coil per institutional standard practice for MRI SCAN 1 only.

6.2 Regulatory Requirements

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). An 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 locally.

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 30 paired evaluable MRI examinations from eligible participants. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any recruitment barriers.

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 institutions.

7.0 DATA MANAGEMENT/ONLINE REGISTRATION

7.1 General

7.1.1 Data collection and management will be performed by the Biostatistic Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine

Gatsonis. The Biostatistics Center (BC) is located at the 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 is available to clinical sites 24 hours a day, seven days a week. A DMC contact list is located on the ACRIN web site (www.acrin.org) for each protocol.

7.2 Clinical Data Submission

7.2.1 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.

7.2.2 To submit data, the appropriate investigator-designated research staff will log onto the assigned URL and supply the pre-assigned user name and password. The user enters data directly into the electronic case report form (eCRF). Various validation checks will be performed to detect errors as data are entered and upon submission of the form. These checks look for data that are missing, data that are out of range, and data that are in the wrong format (e.g., character data in a field requiring numeric responses).

7.2.3 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 is 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. 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 an institution, 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 Quality Assurance (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 eCRFs.

8.0 STUDY PROCEDURES

A total of 30 paired evaluable MRI examinations from eligible participants will be collected at a minimum of 6 participating institutions, representing each of the three major MRI vendors (Siemens, GE, and Philips). Stratification of participants will be equal across vendor platforms (i.e., 10 images from Siemens, 10 from GE, 10 from Philips).

Participants will undergo two 3T MRI studies performed no less than 2 calendar days and no more than 14 days apart. The quantitative imaging studies for the trial (DCE-MRI and DWI) will be performed without the endorectal coil. At the discretion of the participating sites, the initial MRI visit (MRI SCAN 1) may be supplemented with endorectal coil imaging per institutional norms. The imaging protocols and options are described in detail in Sections 8.2 and 8.3 and in ACRIN 6701 Imaging Manual (www.acrin.org/6701_imagingmanual.aspx).

8.1 VISIT 1: Eligibility/Registration Visit

8.1.1 Obtain a signed informed consent form;

8.1.2 Baseline assessment to determine eligibility will comprise the following:

- Obtain and review medical history, including:
  - Baseline abnormalities/pre-existing conditions;
  - Prior surgical history;
  - Blood test results for renal sufficiency; perform a blood test to ensure renal health if not done within 48 hours prior to enrollment;
  - Prior incidence of severe claustrophobia or anxiety;
  - MRI-incompatible metallic objects or implanted medical devices in the body;
  - Confirm prostate cancer diagnosis and minimum tumor burden;

8.1.3 Register the eligible participant.

8.2 VISIT 2: MRI SCAN 1 – Between Day 0 and 28 Days After Visit 1

MRI SCAN 1 should be completed no earlier than 28 days and no more than 90 days after prostate biopsy (TRUS-guided biopsy per Section 5.1.2).

MRI SCAN 1 and MRI SCAN 2 must be completed **no earlier than 2 calendar days (to ensure 24 hours for clearance of gadolinium) and no later than 14 days apart**, and both must be completed prior to treatment initiation.

NOTE: Although the vascular half-life of gadolinium-based contrast agents addressed by the QIBA DCE-MRI profile is approximately 90 minutes, it is required that participants should not have received any gadolinium-based contrast agent within 24 hours before a DCE-MRI procedure as some residual contrast agent may remain in the lesion(s) of interest and the impact of such residual contrast agent on the within-patient coefficient of variation is unknown (QIBA DCE-MRI profile v1.0. 2011).

The same scanner vendor and model must be used for MRI SCAN 1 and MRI SCAN 2. The same contrast agent used for MRI SCAN 1 must be utilized for MRI SCAN 2 (see Section 9.1 for limitations on contrast agents for the trial).

8.2.1 Review medical records for baseline abnormalities/pre-existing conditions prior to the MRI examination;

8.2.2 Prepare participant according to local standard practice, including any pre-treatment for severe claustrophobia and anxiety and review of any presence of MRI-incompatible metallic objects or implanted medical devices in body;

8.2.3 Perform prostate MRI exam, including DWI and DCE-MRI according to procedures for MRI SCAN 1 outlined in Section 9.0 of the protocol and in the ACRIN 6701 Imaging Manual (www.acrin.org/6701_imagingmaterials.aspx).

Imaging procedures are described for those sites electing and declining to include endorectal coil examination. Exact imaging procedure will vary based on local institutional practices for clinical prostate MRI at 3T;

8.2.4 Assessment for AEs (between 24 and 72 hours after the study-related functional MRI). This can be performed either telephone or personal contact.

8.3 VISIT 3: MRI SCAN 2 – No More Than 14 Days After MRI SCAN 1 and Prior to Treatment Initiation

MRI SCAN 2 will be completed **a minimum of 2 calendar days and a maximum or 14 days after** MRI SCAN 1; both scans must be completed prior to treatment initiation.

NOTE: Although the vascular half-life of gadolinium-based contrast agents addressed by the QIBA DCE-MRI profile is approximately 90 minutes, it is required that participants should not have received any gadolinium-based contrast agent within 24 hours before a DCE-MRI procedure as some residual contrast agent may remain in the lesion(s) of interest and the impact of such residual contrast agent on the within-patient coefficient of variation is unknown (QIBA DCE-MRI profile v1.0. 2011).

The same scanner vendor and model must be used for MRI SCAN 1 and MRI SCAN 2. The same contrast agent used for MRI SCAN 1 must be utilized for MRI SCAN 2 (see Section 9.1 for limitations on contrast agents for the trial).

8.3.1 Review medical records for baseline abnormalities/pre-existing conditions prior to the MRI examination;

8.3.2 Prepare participant according to local standard practice, including any pre-treatment for severe claustrophobia and anxiety and review of any presence of MRI-incompatible metallic objects or implanted medical devices in body;

8.3.3 Perform prostate MRI exam, including DCE-MRI and DWI according to vendor-specific procedures and parameters for MRI Scan 2. Anatomic imaging performed during MRI SCAN 1 is not to be replicated during this visit unless deemed necessary for the patients' clinical care (i.e., repetition of clinically important imaging that was deemed to be non-diagnostic during MRI SCAN 1).

Procedures are outlined in Section 9.0 of the protocol, and vendor-specific parameters are detailed in the ACRIN 6701 Imaging Manual (www.acrin.org/6701_imagingmaterials.aspx). All sites will observe similar DCE-MRI and DWI procedures for MRI Scan 2 as for MRI Scan 1;

8.3.4 Assessment for AEs (between 24 and 72 hours after the study-related functional MRI). This can be performed either telephone or personal contact.

NOTE: If the institution's site PI or supervising radiologist deems critical study-related imaging series (for example, axial T1 and T2, DWI, or DCE-MRI at MRI SCAN 1; axial T2, DWI, or DCE-MRI on MRI SCAN 2) to be deficient due to severe technical artifact, scanner/coil failure, severe participant motion, or gadolinium-injection failure, additional visits to repeat the deficient imaging series for MRI SCAN 1 or MRI SCAN 2 are permitted if the participant is willing and able to comply with additional imaging.

Such imaging must adhere to the protocol-specific imaging procedures and take place within 14 days of the non-deficient imaging study.

The site will need to appropriately document all cases in which deficient examinations lead to repetition of imaging. Contact the trial's lead ACRIN data manager for assistance as needed.

8.4 ADDITIONAL IMAGING AND OFF-STUDY CRITERIA

All participants who complete both study-related MRI visits and undergo all required imaging series, including axial T2, DWI, and DCE-MRI imaging, will be considered to have completed their study participation.

The following circumstances will require either additional imaging or replacement of the participant to reach target accrual for the trial:

8.4.1 Locally-Determined Deficient Imaging Study. If the institution's site PI or supervising radiologist deems critical study-related imaging series to be deficient (see additional description in second NOTE in Section 8.3 above), additional visits to repeat the deficient imaging series for MRI SCAN 1 or MRI SCAN 2 are allowed if the participant is willing and able to comply with additional imaging. However:

- Any participants unwilling to complete repeat imaging studies will be off-study and will be replaced to meet trial accrual.
- Repeat imaging must adhere to the protocol-specific imaging procedures and performed within 14 days of the non-deficient imaging study.
- **The site must appropriately document all cases in which deficient imaging lead to repeat of imaging.** Contact the trial's lead ACRIN data manager for assistance as needed.

8.4.2 Incomplete Study MRI SCAN 2. Participants who do not complete the MRI SCAN 2 for any reason, including initiating treatment prior to completion of study-related imaging, will be replaced to meet target accrual.

8.4.3 Centrally-Determined Deficient Imaging Study. A central review for quality will be performed on all MRI SCAN 1 and MRI SCAN 2 series prior to analysis:

- Should MRI SCAN 1 and/or MRI SCAN 2 be deemed technically deficient, an additional participant will be enrolled and imaged to meet target accrual.
- Replacement participants will be accrued at the same participating site with the same vendor equipment, if the participant whose deficient imaging needs to be replaced (in order to maintain accrual of 10 participants to each vendor manufacturer).

8.4.4 Central Diagnostic Review of MRI SCAN 1. Central review prior to quantitative DWI and DCE-MRI analysis will assess the presence and size of all visible tumor nodules. If central diagnostic evaluation of MRI SCAN 1 fails to reveal a definite or likely tumor nodule of 5 mm or greater, a replacement participant will be enrolled to the trial:

- Replacement participants will be accrued at the same participating site with the same vendor equipment, if the participant whose deficient imaging needs to be replaced (in order to maintain accrual of 10 participants to each vendor manufacturer).
- Participants with complete imaging data sets, but whose MRI SCAN 1 does not define a dominant tumor nodule, will be evaluated for the non-tumor endpoints (e.g, whole prostate evaluation for DWI and DCE-MRI).

8.5 Study Procedures Table

Study Procedures	VISIT 1: Eligibility/ Registration Visit	BOTH MRI SCANS FOR THE TRIAL MUST BE COMPLETED NO MORE THAN 14 DAYS APART AND BEFORE TREATMENT INITIATION	
		VISIT 2: MRI SCAN 1 (Between Day 0 and 28 Days After VISIT 1: Eligibility/Registration Visit)	VISIT 3: MRI SCAN 2 (No Earlier Than 2 Calendar Days, But No Later Than 14 Days After VISIT 2: MRI SCAN 1)
Obtain a Signed Informed Consent Form	X		
Perform Screening/Eligibility Review	X		
Review of Medical and Surgical History	X		
Check GFR for Renal Sufficiency	X		
Register Eligible Study Participant	X		
Review Medical Records for Baseline Abnormalities/Pre-existing Conditions Prior to MRI	X	X	X
Prepare Participant Per Institutional Standard Practice as Needed: Pre-medication for Severe Claustrophobia and Anxiety, Assess for Metal in Body		X	X
Insert Intravenous Catheter: Same Size and Placement Recommended for Both Scans		X	X
Administer Gadolinium-Based Contrast Agent* (Same Type and Body-Weight-Adapted Amount for Both Scans, Unless Contraindicated)		X	X
Perform Anatomic MR Imaging Per Institutional Standard Practice		X (with or without endorectal coil)	
Perform Study-Related Functional MR Imaging: DCE-MRI and DWI: Procedures per Section 9.0 and the ACRIN 6701 Imaging Manual**		X (without endorectal coil)	X (without endorectal coil)
AE Assessment§		X	X

***** The same contrast agent used for MRI SCAN 1 must be utilized for MRI SCAN 2 (see Section 9.1 for limitations on contrast agents).

**The same scanner vendor and model must be used for MRI SCAN 1 and MRI SCAN 2.

§ Assessed between 24 and 72 hours via telephone or personal contact after the study-related functional MR imaging.

9.0 IMAGING PROTOCOL

9.1 Imaging Requirements and Parameters

Imaging parameters, including instructions for phantom imaging protocols for trial qualification, are available in the ACRIN 6701 Imaging Manual, available online at www.acrin.org/6701_imagingmaterials.aspx.

For DCE-MRI, FDA-approved small-molecular-weight gadolinium contrast agents without significant protein binding are to be used. The following are examples of exclusions: gadobenate dimeglumide (Gd-BOPTA; MultiHance, Bracco Imaging, S.p.A.) and gadoxetic acid (Gd-EOB-DPTA; Eovist, Bayer HealthCare Pharmaceuticals, Inc.), and blood pool agents (e.g., gadofosveset trisodium [Vasovist, EPIX Pharmaceuticals, Inc.; Ablavar, Lantheus Medical Imaging, Inc.]).

NOTE: If the institution's site PI or supervising radiologist deems critical study-related imaging series (for example, axial T1 and T2, DWI, or DCE-MRI at MRI SCAN 1; axial T2, DWI, or DCE-MRI on MRI SCAN 2) to be deficient due to severe technical artifact, scanner/coil failure, severe participant motion, or gadolinium-injection failure, additional visits to repeat the deficient imaging series for MRI SCAN 1 or MRI SCAN 2 are allowed if the participant is willing and able to comply with additional imaging. Such imaging must adhere to the protocol-specific imaging procedures and take place within 14 days of the non-deficient imaging study.

9.1.1 Initial Site Qualification, Phantom Scanning, and Ongoing QA Procedures

Imaging sites will be selected based on availability of eligible subjects for enrollment, access to an appropriate 3T MRI scanner, and institutional expertise in prostate MRI as defined in Section 6.1. Six (6) imaging centers will be selected for participation based on access to 3T MRI scanners from each of the three major MRI vendors (Siemens, GE, and Philips). Additional centers meeting qualification requirements may join the trial if, in the judgment of trial leadership additional accruing center(s) will aid in the achievement of trial aims.

It is strongly recommended that all trial imaging be performed on a single scanner system, at the very least, all scans must be performed on the same vendor and model scanner. All scanners used must be pre-qualified for participation via phantom imaging. Sites will indicate their intention for non-study related clinical imaging during MRI SCAN 1 (i.e., endorectal coil or non-endorectal coil imaging). This decision will be based on institutional preferences for anatomic 3T MRI of the prostate, and will not affect the acquisition method (i.e., non-endorectal coil) for study-related DWI and DCE-MRI studies.

Phantom Qualification. Prior to accruing patients, each site must first scan and submit data for the DWI and DCE-MRI phantoms based on the phantom scanning protocol described in the ACRIN 6701 Imaging Manual. Phantoms must be scanned, with images submitted to the ACRIN core lab for analysis and approval prior to a site's opening for patient enrollment.

DCE-MRI Phantom for Qualification. When obtaining DCE-MRI clinical trial data across time points, institutions, and MR system vendors, it is critical that the scanners to

be used for such studies be characterized with respect to signal response across an appropriate range of T_1 values representative of those measured from tissue and blood during an actual DCE-MRI acquisition. This is best accomplished using a standardized R1 phantom, which will be used for site qualification and ongoing quality control of scans obtained during the trial. In addition to qualifying sites at the initiation of the study, the data from the standardized phantom can be used to harmonize results, if necessary, across sites and vendor platforms. A multi-compartment phantom, with inserts having T_1 relaxation times spanning the ranges typically obtained in blood and in tissue, will be used for DCE-MRI qualification. Phantom design is based on the recommendations of the RSNA QIBA DCE-MRI Technical Committee (http://qibawiki.rsna.org/images/5/5f/Prototype_Phantom_20100203.pdf).

DWI Phantom for Qualification. An ice-water phantom for DWI will be employed as described by Chenevert et al. (Chenevert, Galbán et al. 2011). This phantom contains an isolated central sealed compartment containing distilled water. This is surrounded by a larger reservoir accessible to the user. The outer reservoir is filled with an ice water mixture, and allowed to come to thermal equilibrium. This ensures a constant temperature of the central reservoir for consistency of the D(t) value.

Rescanning With the Phantom for Maintenance. In addition, the phantom must be rescanned prior to any subsequent patient scan if there are any substantive changes in scanner hardware or software (for example, major upgrade to a new software version). See ACRIN 6701 Imaging Manual for details.

The phantom acquisition protocols are summarized below. The ACRIN 6701 Imaging Manual describes in detail how the DWI and DCE-MRI phantom scans are to be performed, and how phantom data will be assessed to qualify sites for study participation.

9.1.1.1 DWI Phantom Scanning

- Prepare ice-water phantom on site per specified instructions
- Position phantom in center of magnet bore (with local posterior array coils if not table-based), apply local torso array coils to anterior of phantom and landmark to phantom center.
- After localizer scan, perform multi-B-value (B values of 0, 100, 600, and 800 s/mm^2) SE-EPI series in the axial plane as specified in the ACRIN 6701 Imaging Manual (www.acrin.org/6701_imagingmaterials.aspx).

9.1.1.2 DCE-MRI Scanning

- Position phantom at center of magnet with appropriate posterior and anterior local array coils, landmark to center of phantom.
- After localizer scan, perform the following volumetric spoiled gradient echo imaging series groups:
  - Multi-flip angle (for R1 evaluation)
  - Body coil and array coil paired imaging (for surface coil correction)
  - Stability test

All enrolled subjects will undergo two successive MRI studies, no greater than 14 days apart. MRI SCAN 1 (Visit 2) will encompass the institutional-specific standards for a clinical anatomic MRI study (with or without endorectal coil). MRI SCAN 2 will comprise modified anatomic scanning for localization purposes only, followed by study-specific DWI and DCE-MRI imaging, all without the endorectal coil.

Separate imaging protocols are provided for MRI SCAN 1 based on institutional preferences for endorectal coil or non-endorectal coil anatomic imaging. All imaging at MRI SCAN 2 will be solely for trial research purposes, and will be performed without endorectal coil at all sites. Exceptions to this include cases where the local study radiologist, having reviewed MRI SCAN 1, deems that the participant may benefit clinically from additional scanning during MRI SCAN 2 so as to supplement sub-optimal imaging obtained at MRI SCAN 1. Additional imaging during the MRI SCAN 2 visit (including endorectal coil imaging, if appropriate) may then be obtained.

9.1.2 MRI Procedures Excluding and Including the Endorectal Coil

9.1.2.1 MRI SCAN 1 Imaging Procedures: Endorectal Coil *EXCLUDED* (VISIT 2)

9.1.2.1.1 Weigh the participant, and document body weight;

9.1.2.1.2 Pre-draw the appropriate amount (0.1 mmol/kg) of study-approved gadolinium-based contrast agent (see Section 9.1) and 20 mL normal saline into dual-chamber power-injector in preparation for DCE-MRI study. Document the amount of contrast administered;

9.1.2.1.3 Place intravenous line (20G or higher) for gadolinium contrast administration—document injection site and catheter size;

9.1.2.1.4 Place patient supine in MRI scanner; connect IV to power injector; and deploy scanner-specific local torso array coils about pelvic region;

9.1.2.1.5 Landmark patient at the level of the symphysis pubis;

9.1.2.1.6 Complete pre-contrast anatomic imaging as described below. (Minimal required imaging is listed. Additional imaging series per institutional norms are allowed):

- Localizer, per institutional routine;
- T1-weighted axial imaging;
- T2-weighted axial imaging;
- T2-weighted coronal imaging;

9.1.2.1.7 Complete protocol-specific multi-B value axial SE-EPI DWI sequence, with B values of 0, 100, 600, and 800 s/mm^2);

9.1.2.1.8 Initiate DCE-MRI acquisition protocol according to vendor-specific model/version requirements available in the ACRIN 6701 Imaging Manual, including:

- Axial multi-flip-angle T1 mapping protocol;
- Body coil only imaging for receive coil bias field calculation;

- Dynamic enhanced imaging:
    - After beginning of dynamic enhanced series, bolus gadolinium contrast agent and normal saline flush is administered;

9.1.2.1.9 After completion of DCE-MRI imaging, optional additional post-gadolinium imaging may be obtained per institutional norms.

9.1.2.2 MRI SCAN 1 Imaging Procedures: Endorectal Coil *INCLUDED* (VISIT 2)

9.1.2.2.1 Weigh the participant, and document body weight;

9.1.2.2.2 Pre-draw the appropriate amount (0.1 mmol/kg) of FDA-approved gadolinium-based contrast agent and 20 mL normal saline into dual-chamber power-injector in preparation for DCE-MRI study. Document the amount of contrast administered;

9.1.2.2.3 Place intravenous line for gadolinium contrast administration—document injection site and catheter size;

9.1.2.2.4 Deploy endorectal coil per institutional routine;

9.1.2.2.5 Place patient supine in MRI scanner; connect IV to power injector; and deploy additional scanner-specific local torso array coils about pelvic region;

9.1.2.2.6 Landmark patient at the level of the symphysis pubis;

9.1.2.2.7 Perform endorectal coil anatomic imaging (minimum required imaging for the study is listed below; additional imaging series per standard institutional practices are allowed):

- Localizer, per institutional routine;
- T1-weighted axial imaging;
- T2-weighted axial imaging;
- T2-weighted coronal imaging;

9.1.2.2.8 Remove endorectal coil from patient while in scanner suite. Return patient to supine positioning; re-landmark to symphysis pubis;

9.1.2.2.9 Complete protocol-specific multi-B value axial SE-EPI DWI sequence, with B values of 0, 100, 600, and 800 s/mm2);

9.1.2.2.10 Initiate DCE-MRI acquisition protocol according to vendor-specific model/version requirements available in the ACRIN 6701 Imaging Manual, including:

- Axial multi-flip-angle T1 mapping protocol;
- Body coil only axial imaging for receive coil bias field calculation;
- Dynamic enhanced imaging :
    - After beginning of dynamic enhanced series, bolus gadolinium contrast agent and normal saline flush is administered;

9.1.2.2.11 After completion of DCE-MRI imaging, optional additional post-gadolinium imaging may be obtained per institutional norms.

9.1.2.3 MRI SCAN 2 Imaging Procedures: Endorectal Coil *EXCLUDED* (VISIT 3)

9.1.2.3.1 Weigh the participant, and document body weight;

9.1.2.3.2 Pre-draw the appropriate amount (0.1 mmol/kg) of FDA-approved gadolinium-based contrast agent and 20 mL normal saline into dual-chamber power-injector in preparation for DCE-MRI study. The same contrast agent used for MRI SCAN 1 must be utilized for MRI SCAN 2. Document the amount of contrast administered;

9.1.2.3.3 Confirm injection site and catheter size used for MRI Scan 1 and replicate for MRI Scan 2 unless contraindicated due to injury from MRI SCAN 1 IV placement;

9.1.2.3.4 Place intravenous line for gadolinium contrast administration;

9.1.2.3.5 Place patient supine in MRI scanner; connect IV to power injector; and deploy scanner-specific local torso array coils about pelvic region;

9.1.2.3.6 Landmark patient at the level of the symphysis pubis;

9.1.2.3.7 Complete pre-contrast imaging:

- Localizer, per institutional routine;
- T2-weighted axial imaging;

9.1.2.3.8 Complete protocol-specific multi-B value axial SE-EPI DWI sequence, with B values of 0, 100, 600, and 800 s/mm2);

9.1.2.3.9 Initiate DCE-MRI acquisition protocol according to vendor-specific model/version requirements available in the ACRIN 6701 Imaging Manual, including:

- Axial multi-flip-angle T1 mapping protocol
- Body coil only axial imaging for receive coil bias field calculation
- Dynamic enhanced imaging
    - After beginning of dynamic enhanced series, bolus gadolinium contrast agent and normal saline flush is administered.

9.2 Images Submission

9.2.1 For TRIAD Submission: The preferred image transfer method is via TRIAD, a software application that ACRIN provides for installation on a site's PC. One or several computers of choice within the institutional "firewall" and on the institutional network may be equipped with TRIAD software; Internet access is also 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 anonymizes, encrypts, and performs a lossless 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.

9.2.2 For Submission Via Media: In the event that the transfer of image data is not available via TRIAD, images may also be sent on a CD/DVD-ROM to the ACRIN core lab for transfer to the image archive. All image data submitted to the ACRIN core lab must be in DICOM format.

The Image Transmittal Worksheet (ITW) for all MR images must be completed electronically and a hard copy must accompany all media submissions. PDF versions of the transmission worksheets are available for downloaded at www.acrin.org/6701_imagingmaterials.aspx.

9.2.3 Images may be mailed to:

American College of Radiology Imaging Network
MR/CT Core Laboratory
Attn: ACRIN 6701
1818 Market Street 16th floor
Philadelphia, PA 19103

9.3 Local Site Review of Imaging

All imaging studies should be evaluated by the research MRI technologist during the study. Non-contrast enhanced series that are deemed suboptimal may be repeated by the technologist during the course of the study if the cause of image degradation is discovered and can be corrected. Such replications of imaging series should be documented appropriately (for guidance, contact ACRIN Data Management)

After completion of imaging for MRI SCAN 1, the study should be reviewed based on standard institutional practices for clinical image review and reporting. The site PI/radiologist also must review this imaging prior to MRI SCAN 2, to determine:

1) The clinical adequacy of the examination for prostate cancer detection and staging;
2) The technical adequacy and adherence to protocol specifications for anatomic, DWI, and DCE-MRI sequences. Technical issues during the trial should be reported to the ACRIN core lab to ensure issues do not impact additional participants' imaging studies. Protocol deviations from the trial specifications will need to be reported to ACRIN Data Management.

If the standard practice anatomic sequences of MRI SCAN 1 are is deemed suboptimal for clinical evaluation, the site PI/radiologist has the discretion to recommend repeat of one or more clinical imaging series during MRI SCAN 2.

Similarly, if the study-specific DWI and/or the DCE-MRI sequences of MRI SCANS 1 or MRI SCAN 2 are deemed technically inadequate or not per protocol specifications, the site PI/radiologist and/or ACRIN has the option to recommend repetition of study sequences as a separate visit. Only willing participants will undergo additional imaging visits. See the NOTE in Section 9.1 for details.

9.4 Central QC of MRI SCANS 1 and 2 (VISITS 2 and 3): DWI and DCE-MRI Studies

ACRIN core lab personnel will review the image sets for protocol compliance. All protocol deviations will be noted (and the site will need to formally submit a protocol deviation form to ACRIN Data Management), and images that are deemed to be non-compliant will be excluded from analysis. Image sets also will be reviewed for technical adequacy, including adequate image signal-to-noise ratio, absence of severe artifacts, and absence of severe patient motion. In cases where image sets are judged to be substandard, ACRIN core lab personnel, in conjunction with the study PI, will make a final determination regarding whether the image sets are analyzable in whole or in part. All images deemed analyzable by the ACRIN core lab and the site PI will be evaluated for DWI and DCE-MRI segmentation.

9.5 Central Reader Evaluation

All images will be reviewed centrally by two radiologist readers with experience in DCE-MRI and DWI. Readers will analyze each study independently, without knowledge of the results of the other reader. The central read will entail three distinct portions:

1) Review of MRI SCAN 1 imaging for tumor detection;
2) Combined review of MRI SCAN 1 and MRI SCAN 2 DWI sequences for tumor and prostate segmentation; and
3) Combined review of MRI SCAN 1 and MRI SCAN 2 DCE-MRI for tumor and prostate segmentation.

9.5.1 MRI SCAN 1 (VISIT 2): Review for Tumor Detection

Each reader will initially review the anatomic imaging (axial T1 and T2) to determine the presence of absence of visible tumor nodules. Only nodules 5mm or more in longest linear dimension will be noted. Readers will indicate the presence of tumor in each of six sextants (left base, left mid-gland, left apex, right base, right mid-gland, and right apex). Readers also will score the degree of hemorrhage in each of these sextants. The dominant tumor nodule, if visible, will be indicated and measured in two dimensions. Readers also will determine the presence or absence of tumor extension into the extracapsular tissues, and the seminal vesicles.

In the same reader session, the reader will evaluate the anatomic imaging in combination with the DWI and DCE-MRI, and re-evaluate the likelihood of tumor in each sextant. As a result, the reader will determine whether or not a dominant tumor nodule of 5 mm in longest diameter is or is not present.

If a tumor nodule of sufficient size is not detected by each of the two central readers, this study will be rated as a "no dominant tumor nodule present". Such an event will necessitate accrual of an additional patient (from a site with the same MRI vendor). These cases will continue to be evaluated for whole prostate segmentation.

9.5.2 MRI SCANS 1 and 2 (VISITS 2 and 3): DWI Segmentation

Each reader will evaluate the DWI studies, including all B value images and the D(t) image map, Image review will be undertaken on a dedicated viewing station running specialized software developed at the University of Pennsylvania oncologic MRI core laboratory. Imaging from MRI SCANS 1 and 2 will be reviewed concurrently. Readers

will have access to the anatomic imaging from MRI SCAN 1, as well as their tumor nodule assessment during this review.

Each reader will be asked to outline the whole prostate and, when visible, the dominant tumor nodule. In cases where more than one discrete nodule are seen, the largest nodule will be chosen. Outlines will be drawn for each slice that the prostate (or tumor) is visualized, using viewing and segmentation software at the University of Pennsylvania oncologic MRI core laboratory. Segmentation volumes of interest (VOIs) will be saved electronically in multiple 2D region of interest (ROI) files in IDL format. These segmentations, with basis series, time and reader stamp, will be converted to separate DICOM images with sets with binary masking of prostate or tumor, for electronic submission and storage at ACRIN.

9.5.3 MRI SCANS 1 and 2 (VISITS 2 and 3): DCE-MRI Segmentation

Central reader segmentation of DCE-MR images will proceed in a manner similar to that of the DWI segmentation. Specialized IDL viewing software will be provided that will allow for multi-phase viewing of the DCE-MR images sets, including individual baseline, multi-phase baseline averaged, and individualized and multi-phase averaged post-gadolinium images, with selection of the phase(s) of interest adjustable by the reader. Subtraction imaging options also will be available. Readers will have access to the anatomic imaging from MRI SCAN 1, as well as their tumor nodule assessment during this review.

Readers will segment the whole prostate and the dominant tumor nodules, using the same scheme as described in Section 9.5.2 above. Readers will not have access to functional image masks (e.g., K^{trans}, $IAUGC90^{bn}$, etc.) during the image segmentation. VOI sets for whole prostate and dominant tumor will be saved in IDL format and converted to binary DICOM image masks for electronic submission and storage at ACRIN.

Arterial input functions will not be derived by radiologist readers at the site or centrally, but will instead be automatically calculated by software developed at the University of Pennsylvania oncologic MRI laboratory, using a variation of the schema previously described (Chen, Yao, Thomasson. 2008).

9.6 Computation of DWI and DCE-MRI Metrics

9.6.1 DWI Metrics

Computational functional imaging maps from the multi B-value DWI images will be computed at the University of Pennsylvania oncology MRI laboratory. Reader derived segmentations will be overlaid on the functional maps. Histogram analysis will be undertaken to determine mean, median, as well as 10^{th} and 90^{th} percentile values. For trial endpoints, median values of all pixels in the segmented reader VOIs will be utilized.

9.6.2 DCE-MRI Metrics

This study will evaluate two methods for K^{trans} and $IAUCG90^{bn}$ calculation. The primary methodology, which will be applicable to Aims 3.1.1, 3.1.2, 3.2.1.1, and 3.2.1.2 will be the traditional T1-dependent analysis based on Bloch equation formula for T1 signal intensity of spoiled gradient echo (SPGR) imaging. This method will utilize the variable

flip angle maps collected at all patient-timepoints to determine native (pre-gadolinium) tissue T1 as an input to the Bloch equation for calculation of estimated tissue gadolinium concentration versus time.

DCE-metrics will also be calculated for all DCE-MRI exams using the T1-independent (linear approximation) method. In this calculation, the (bias field corrected) signal intensity of tissue or blood following gadolinium is assumed to be a linear function of gadolinium concentration, simplifying the derivation of DCE-MRI metrics. This evaluation, to be performed at all patient-timepoints, will be utilized for the secondary endpoint to compare the repeatability coefficient for K^{trans} as obtained via the T1-dependent or T1-independent methods.

The DCE-MRI time course image sets will be converted to estimated tissue gadolinium maps. Using these maps, the participant-specific AIF input function will be created. This AIF will be utilized to create DCE-MRI parametric image sets using the modified two-compartment model for estimation of gadolinium (Tofts, Brix et al. 1999), with least-square minimization techniques, run on in-house software routines in IDL at the University of Pennsylvania oncologic MRI core laboratory. Parametric maps for K^{trans}, k_{ep}, v_e, v_p, and $IAUCG90^{bn}$, will be created.

Bias field corrected images will be based on the paired array coil and body coil image sets. Parametric maps for K^{trans}, k_{ep}, v_e, v_p, and $IAUCG90^{bn}$ will be created in a similar manner.

To generate pertinent DCE-MRI values for whole prostate and tumor, reader derived segmentations will be overlaid on the functional maps. Histogram analysis will be undertaken to determine mean, median, as well as 10^{th} and 90^{th} percentile values. For trial endpoints, median values of all pixels in the segmented reader VOIs will be utilized.

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 imaging 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(s), 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 Study-Related Adverse Events

Only AEs that are considered **possibly, probably,** or **definitely** related to the study-related MRI scan procedures require reporting to ACRIN. Please refer to your local IRB's policies regarding AEs.

10.6.1 Expected Adverse Events Associated With IV Needle Placement

- Hemorrhage (hematoma at the injection site);
- Phlebitis;
- Minor discomfort;
- Bleeding;
- Infection;
- Bruising.

10.6.2 Expected Adverse Events Associated With Gadolinium Contrast Agent

- Nausea;
- Headache;
- Hives;
- Temporary low blood pressure;
- Allergic reaction;
- *Rare, but Serious:* Kidney impairment, details follow.

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

Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD), kidney disorders, may occur in patients with moderate to end-stage kidney disease (glomerular filtration rate < 30 mL/min/1.73m^2) and in patients with renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period after they have had a MRI scan with extracellular gadolinium-based MR contrast agents (GBMCA) that do not have dominant hepatobiliary excretion.

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

10.6.3 Expected Adverse Events Associated With MRI

- Anxiety/stress;
- Claustrophobia;
- Discomfort.

10.6.4 Expected Adverse Events With the Endorectal Coil (Used Per Institutional Standard Practice During MRI Scan[s])

Likely

- Possible "warming" sensation from the endorectal coil.
- Mild discomfort from insertion.

Less Likely, but Serious

- Hemorrhage/bleeding.

Rare

- Localized heating of the body.

10.7 Source Documentation of Adverse Events

At each contact (site 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 to MRI, and SAEs will be documented in the study participant's chart and AE eCRFs, 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 eCRF 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) 574-3183** 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 gadolinium administration and/or MRI scan 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 of AEs on source documents and the AE case report form (eCRF), 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 (AdEERS).**

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 imaging with the severity level of grades 3, 4, 5 that occur during study participation and up to 24 hours after the study procedure. See Table 1 below for additional details. Local IRBs and/or institutions may stipulate additional AEs reporting based upon their review of the protocol.

TABLE 1. Expedited Reporting Requirements for Adverse Events that Occur Within 24 Hours of the Administration of Gadolinium[1]

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 AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 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

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 AdEERS within 24 hours of learning of the event, followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
- "10 calendar days"—A complete AdEERS 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 patient 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 occurring during study participation and up to 24 hours after the 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 eCRF).

10.10.3 All life-threatening/disabling unexpected AEs (considered possibly, probably, or definitely related to the MRI study) occurring during study participation and up to 24 hours after the study procedure will 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 eCRF).

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 the MRI study must be reported within ten (10) working days of first knowledge of the event, in addition to documentation in participant chart and AE eCRF.

10.10.5 All other SAEs with attribution of possibly, probably, or definitely related to the MRI study which include AEs that results in persistent or significant disability or incapacity, or congenital anomaly (birth defect) in the offspring of the study participant must be reported within ten (10) working days of first knowledge of the event during study participation and up to 24 hours after the study procedure, in addition to documentation in participant chart and AE eCRF.

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) 897-1704

- 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 AdEERS must be submitted per the protocol-specific requirements or the regulatory reporting timelines, if not specified in the protocol.

10.10.8 Completion of AdEERS

All SAEs that occur within 24 hours of gadolinium administration for the MRI study require the submission of an electronic AdEERS report within five (5) calendar days of first knowledge of the event is required.

AdEERSMD 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 event that the electronic system is down, the AdEERS report must be faxed to the following:

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

ACRIN contact to confirm receipt of AdEERS 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) 496-0737**, 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 AdEERS 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 6701 QIBA
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 (see Appendix I for an ICF template). 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 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. 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 eCRFs. 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 (electronic and paper copies) 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 institutions 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 an institution 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 institutions 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 eCRFs. 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 electronic and paper, are the primary data collection instruments for the study. The paper copies of eCRFs are provided as tools to the sites; they are not mandated to be used on site. If sites do use ACRIN-supplied paper copies of eCRFs, 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 eCRFs must be recorded, and any missing data must be explained. If a space is left blank on paper copies of eCRFs 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 copies of eCRFs must be printed legibly in black ink on the paper

copies of eCRFs. 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 eCRFs 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 paper copies of eCRF 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 the paper copies of eCRFs are to be used as source documentation at the time of data collection, then 1) a Note to File should indicate that the ECRF 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 eCRF, the confirmation sheet should be printed out, signed and dated by the person completing the eCRF, and filed as a source document. Any use of paper copies of approved eCRFs as source documentation require a signature and date on the paper copies of the eCRF with a reference to the information source (participant questionnaire, CT, MR, etc.). Any use of paper copies of eCRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a major protocol deficiency.

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Design and Endpoints

The study design is outlined in the Schema. Participants will undergo two successive pre-treatment 3T MRI studies performed within 14 days of each other (with a minimum of 2 calendar days between scans). A central reader study will be conducted where each of two readers will examine the two successive scans. The primary endpoint of this study is repeatability assessment of DCE-MRI metrics K^{trans} and blood-normalized initial area under the gadolinium curve ($IAUGC90^{bn}$) and the DWI metric D(t). The repeatability coefficient (RC) and its 95% confidence interval (CI) will be estimated for each metric (Barnhart and Barboriak, 2009)

15.1.1 Specific Aims and Analysis Plans

15.1.1.1 Primary Aims

15.1.1.1.1 *Determine the test-retest performance, assessed by the RC of K^{trans} and $IAUGC90^{bn}$ and measured by median pixel values of the whole prostate.*

We will conduct the primary analysis with log-transformed whole prostate K^{trans} to make its histogram look more normally distributed. The RC will be estimated by 2.77 times within-subject standard deviation (wSD). To calculate the wSD, we will use a two-way analysis of variance (ANOVA) by expressing K^{trans} value examined by a specific reader on a particular participant as the sum of a random subject effect, a random reader effect, a

random subject-reader interaction effect, and a random error. Note that the variance of a random error indicates the within-subject variability. The within-subject means of squares (WMS) will be derived from the fitted ANOVA model, and wSD can be calculated by the square root of the WMS. Next, the 95% CI for RC (RC^{LL}, RC^{UL}) will be derived by making use of the chi-squared distribution for the WMS.

We will conduct similar analysis for the $IAUGC90^{bn}$. Based on prior literature reports, we do not expect to require log-transformation of the $IAUGC90^{bn}$ data.

15.1.1.1.2 *Determine the test-retest performance, assessed by the RC of D(t) and measured by median pixel values of the whole prostate.*

We will repeat similar analysis for whole prostate D(t) and estimate the RC and its associated 95% CI. As with $IAUGC90^{bn}$, we do not expect to require log-transformation of the D(t) data.

15.1.1.2 Secondary Aims

15.1.1.2.1 *Determine the test-retest performance, assessed by the RC of K^{trans}, $IAUGC90^{bn}$, and D(t), and measured by median pixel values of the prostate tumor.*

Similar to the analysis for the primary aims, we will estimate the RCs for K^{trans}, $IAUGC90^{bn}$, and D(t) for the prostate tumor and their 95% CIs.

15.1.1.2.2 *Determine the effect of reader on the RC of DCE-MRI and DWI metrics for whole prostate and tumor nodule target lesion.*

First, we will utilize the two-way ANOVA models for the whole prostate K^{trans} ($IAUGC90^{bn}$ or D[t]) in which the K^{trans} ($IAUGC90^{bn}$ or D[t]) measure will be written as the sum of a random subject effect, a random reader effect, a random subject-reader interaction effect, and a random error. Noting that the variance of a random reader effect reflects the inter-reader variability, we will test whether its variance is zero by conducting an F test. Second, we will calculate the RCs of the two scans (MRI SCAN 1 and MRI SCAN 2) examined by (1) reader 1 only (2) reader 2 only; and (3) different readers (reader 1 for MRI SCAN 1, reader 2 for MRI SCAN 2, or vice versa). We will then compare these three RC values with the RC values calculated for the primary aims which account for both readers.

We will conduct similar analysis for tumor nodule target lesion.

15.1.1.2.3 *Determine whether T1-dependent or T1-independent methods for gadolinium quantification produce differing values for the RC for K^{trans}.*

To determine whether the RC by T1-dependent method is different from the RC by T1 independent method, we can test if the within-subject variances by the two methods are the same. To this end, we will make use of the WMSs obtained from ANOVA models.

The WMSs for the two methods are the function of the difference (say, *Diff*) between the observed measurement for the *i*th subject by the *j*th method at *k*th scan and the average reading for the *i*th subject by the *j*th method over the replicated scans (*i*=30, *j*=2, *k*=2). We will conduct the paired t-test for the absolute value of the above *Diff* to assess whether the within-subject variances are significantly different between the two methods.

15.1.1.3 Exploratory Aim

15.1.1.3.1 *Explore the correlation between DCE-MRI and DWI metrics for both whole prostate and dominant tumor nodule as target lesions.*

Pearson's correlation coefficients as well as Spearman's rank correlation coefficient between DCE-MRI and DWI metrics will be calculated for both whole prostate and dominant tumor nodule.

15.2 Sample Size/Accrual Rate

The planned sample size is 30 paired evaluable MRI examinations from eligible participants to be accrued over two years from a minimum of six institutions. Each of the three major MRI vendors (Siemens, General Electric, and Philips) will be represented by at least two institutions each. We will control enrollment to ensure that the evaluable exams are equally distributed across the three vendors. However, the study is not designed to examine differences in RC for DWI or DCE-MRI between vendors. Evaluable MRI series will comprise complete data sets with acceptable image quality based on central-assessment as outlined in Section 8.4.

Sample size was chosen so as to provide a reasonably narrow 95% CI about the measured RC for each metric. The upper limit of the 95% CI for RC (RC^{UL}) provides an estimate of the minimal change that can be reliably detected in a given patient (Barnhart and Barboriak, 2009). Our goal is to determine whether the RC^{UL} for a given metric is less than the minimal change that is felt to reflect significant biologic effect in tumors.

15.3 Sample Size Consideration

To guide the sample size selection in this protocol, we have chosen to assign pre-specified minimum changes in each DCE-MRI/DWI metric that one wishes to be able to reliably detect. These minimal changes are those suggested to indicate clinically significant effects, based on literature reports in treatment scenarios where DWI and/or DCE-MRI may be used. Percent change in K^{trans} is evaluated to reflect the use of log-transformed data in test-retest analyses of this metric. Changes in $IAUGC90^{bn}$ and D(t) are assessed in absolute units.

A decline in tumor K^{trans} of approximately 40% or more has been detected when there is effective anti-vascular therapy (Dowlati, Robertson, et al. 2002; Flaherty, Rosen, et al. 2008; Galbraith, Maxwell et al. 2003; Hahn, Yang et al. 2008), which translates to 0.22 change in log-transformed units of K^{trans}.

Effects on IAUCG90 are somewhat more blunted, based on the correlation between K^{trans} and IAUGC90 at relevant values of v_e (Walker-Samuels, Leach, and Collins. 2006.). As such, declines in "area-under-the-curve" assessments of gadolinium tumor accumulation reflective of effective anti-vascular therapy will results in a decline approximately 20%, or roughly 0.05 absolute normalized units (based on an assumed average tumor value for $IAUGC90^{bn}$ of 0.25). For DWI, increases in tumor diffusion constant of 0.3 x 10^{-3} mm^2/sec or greater have been shown after effective therapies (Eccles, Haider et al. 2009; Dudeck, Zeile et al. 2008).

In Tables 1 through 3, we calculate, as a function of potentially observed RCs (i.e. expected RC), the sample size required to ensure that the RC^{UL} for each quantitative MRI metric remains below the pre-defined biologically significant change for that metric (with the number of replication per subject set to 2). The choice of expected RCs is based on prior observations. For example, Ashton et al. demonstrated a measured CV for K^{trans} in the range of 11% to 19% (Ashton, Raunig et al. 2008), and a repeatability of tumor D(t) of 0.17 x10^{-3} mm^2/sec has been reported in Koh et al (Koh, Blackledge et al. 2009).

Table 1. Estimated Sample Sizes for K^{trans}

Significant Change*	Expected RC	Sample Size
0.22	0.125	10
	0.15	19
	0.155	22
	0.16	26
	0.164	***30***
	0.17	37
	0.175	46

* In log-transformed units

Table 2. Estimated Sample Sizes $IAUGC90^{bn}$

Significant Change*	Expected RC	Sample Size
0.05	0.02	5
	0.025	8
	0.03	12
	0.037	***30***
	0.04	48

* In absolute (normalized) units

Table 3. Estimated Sample Sizes for D(t)

Significant Change (x 10^{-3} mm^2/sec)	Expected RC (x 10^{-3} mm^2/sec)	Required Sample Size
0.3	0.17	10
	0.19	14
	0.21	22
	0.224	***30***
	0.23	36

These calculations suggest that an N of 30 should be sufficient to determine an RC^{UL} defining a minimal detectable change at or below a defined threshold of clinically relevant therapy-induced changes.

However, if our study instead defines a higher than expected RC for any of the MRI metrics, we will still be able to define the RC^{UL}, suggesting a threshold for minimal detectable change not explained by measurement variability.

15.4 Reporting Guidelines

15.4.1 Routine Reporting

Routine reports for this protocol will be included in the ACRIN Biostatistics Center Mid-Year and Year-End Updates and will be provided to oversight bodies, including DSMC for review during each of its twice-yearly meeting.

Routine reports will include:

- Accrual and participant characteristics;
- Timeliness and completeness, eligibility and protocol compliance, and outcome data;
- All reported AEs.

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APPENDIX I

ACRIN 6701

INFORMED CONSENT FORM TEMPLATE

Repeatability Assessment of Quantitative DCE-MRI and DWI: A Multicenter Study of Functional Imaging Standardization in the Prostate

<<Note: The American College of Radiology Imaging Network (ACRIN) complies with the privacy measures put forth by the Health Insurance Portability and Accountability Act (HIPAA). However, ACRIN does not monitor compliance with HIPAA; that is the responsibility of the local institutions and their Institutional Review Boards (IRBs). Local IRBs may choose to combine the authorization elements in the informed consent.>>

This is a clinical trial, a type of research study. If you are eligible to participate in this study, your study doctor will explain this clinical research study to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor or other research staff for more explanation. If you decide to do this study, you will be asked to sign and date this form.

The National Cancer Institute (NCI) booklet "Taking Part in Cancer Treatment Research Studies" is available to you. It can be found online at: www.cancer.gov/clinicaltrials/Taking-Part-in-Cancer-Treatment-Research-Studies.

You are being asked to be in this trial because:

1) Recent biopsy results suggest you have prostate cancer;
2) Your treating doctor is referring you for a magnetic resonance imaging (MRI) scan to determine the size, location, and extent of your prostate cancer in order to make proper decisions regarding your treatment.

If you agree to participate in the trial, you will have two MRI scans taken within a two week period to test how similar the two scans are in imaging your prostate.

WHY IS THIS STUDY BEING DONE?

MRI scans are being used more and more to help treating doctors define cancer types, and to define if and how cancer is responding to treatment. Researchers are working to make sure the results from MRIs are as accurate as possible. This study is designed to compare two MRI scans of the prostate area. The MRI studies will be performed using instructions, created by experts in MRI technology, specific to the type of MRI machine being used. The two MRI scans will be performed within two weeks of each other but before treatment begins. The researchers hope to show that the two MRI scans provide similar views of the prostate and any disease that is found.

The first MRI scans is part of your routine standard of care. The second MRI scan is being performed because you have agreed to be in the study. Your treatment could be delayed by 2 to 14 days due to scheduling and the addition of the second MRI scan. Your treating doctor will see the results of the first MRI scan per standard of care. They will not see the results from the second MRI.

About MRI Scans

An MRI uses a powerful magnet and radio waves linked to a computer to create clear and detailed cross sectional images of the body. The MRI scan will provide images of your prostate and any cancer that remains after your biopsy for the study doctors to examine.

About Contrast Agents

Contrast agents are liquid-like dyes that is given via a small intravenous (IV) line placed in a vein in your arm to help imaging machines create pictures of the body's organs and bones. Gadolinium is commonly used with MRI scans to help more clearly show abnormalities and disease that might be less visible without the contrast agent.

About the MRI Scans for This Study

Researchers want to test two MRI techniques in this study. The first, called dynamic contrast-enhanced MRI, or DCE-MRI, uses an imaging contrast agent to track the blood flow in body organs and tumors. The second, called diffusion weighted imaging, or DWI, tracks the motion of water in body organs and tumors. Tumors sometimes show abnormal blood flow and water motion. Both of these MRI techniques will be studied in this trial. Both the first and second MRI scans will use the contrast agent, gadolinium, for the DCE-MRI part of the MRI scan. Your kidney health will be tested before the MRI scans to help make sure the gadolinium will not harm you.

About Use of the Endorectal Coil During MRI

In some institutions, radiologists use a device called an endorectal coil as part of the prostate MRI scan. The endorectal coil allows for more-detailed MRI pictures of the prostate to be taken. The endorectal coil is placed into the rectum during the examination. Your treating doctor will decide whether the endorectal coil will be used for your MRI scan, and can explain more about this procedure.

If the endorectal coil is used, it will only be used during the first MRI scan, the standard of care MRI scan. The endorectal coil will only be used during your second MRI scan if your treating doctor needs to repeat a portion of the endorectal coil imaging that was not useable from your first MRI scan. He/she will discuss any additional images that need to be taken during your second MRI scan. At this time, your treating doctor will let you know if an endorectal coil placement is needed during the second MRI scan, especially if the repeat images will improve imaging results for clinical use.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

A total of 30 people at approximately 6 participating sites will participate in the trial.

HOW LONG WILL I BE IN THE STUDY?

Your participation in the study will begin when you sign the consent form to study participation, and will end after you have completed your second MRI scan. Most participants will be in the study for no more than a month, depending on the time between enrollment and the first MRI study.

This trial is expected to end after all participants have completed the study-related visits and all information has been collected. This study may be stopped at any time by your study doctor, ACRIN, Food and Drug Administration (FDA), or National Cancer Institute (NCI) without your consent because:

- Your health or safety may be at risk;
- You have not been following study instruction;
- Of an administrative decision by ACRIN, the study doctor, FDA, or NCI.

These actions do not require your consent, but you will be informed of any of these decisions if such a decision is made.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your treating doctor first. Choosing to withdraw from the study will not interfere with your future care.

If new information becomes available and this information suggests the procedure will be ineffective or unsafe, you will be notified immediately.

WHAT AM I BEING ASKED TO DO IN THE STUDY?

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

Eligibility and Registration Visit (VISIT 1)

- After signing this consent document, research staff will check your medical history to collect data on your prostate disease.
- Before any study-related imaging can take place, study doctors want to make sure your kidneys are healthy. If your kidney health has not been checked recently, then a blood draw will be needed to test your kidney function. If your results show concerns with your kidney function, you will not be able to participate in the study.
- Research staff will ask you about your history with MRI scans, such as whether you have certain types of metal or metallic devices in your body or have had any trouble with claustrophobia or anxiety in the machine.

1st MRI Scan (VISIT 2)

- Within 0 to 28 days after you join the trial, you will answer some questions about your current health and then complete your 1st MRI scan for the study. This will be the MRI that you would have gotten even if you had not joined the study. Again, gadolinium contrast will be used for the study-related imaging.

2nd MRI Scan (VISIT 3)

- Within 2 calendar days to 14 days after your 1st MRI scan, you will answer some questions about your current health and then have a 2nd MRI scan for the study. This MRI is for the purpose of the study only, and also will include gadolinium contrast. Unless portions of your 1st MRI scan need to be repeated, then only the DCE-MRI and DWI techniques for the study will be completed for the 2nd MRI scan.

Repeat/Additional Imaging

There is a chance that when your study doctor reviews the DWI or DCE-MRI scans and determines that these images may not be interpretable, incomplete, or have other problems that make them unusable for the study, your study doctor will ask if you are willing to have another MRI scan to make sure we have the correct images for the trial. Your study doctor will explain the risks of having an additional contrast-enhanced MRI or other imaging if it is necessary. If you agree to the repeat/additional imaging, you will need to wait at least 2 calendar days after your last contrast scans.

A study chart explains what is expected of you at each study time point.

STUDY CHART

VISIT 1: Eligibility and Registration	• Read and sign this informed consent form (ICF); • Inform research staff of any history of severe claustrophobia or anxiety during MRI scans and of any metal or implanted device in your body; • Have blood drawn to test your kidney health, if not available from within 48 hours before joining the study.
VISIT 2: First MRI SCAN **Within 0 to 28 days after joining the study** ***Before Treatment***	• Follow the instructions your treating and study doctors gave you to prepare for your MRI scan; • Tell research staff about any pre-existing conditions (health concerns) you may have; • Have a small intravenous (IV) line placed for contrast administration; • Receive gadolinium contrast; • Complete an MRI scan that includes study-related techniques; • Talk to your study doctor or research staff and tell them how you are feeling after your MRI scan. They will contact you between 24 – 72 hours after your MRI scan.
VISIT 3: Second MRI SCAN **Within 2 calendar days to 14 days after the 1st MRI scan** ***Before Treatment***	• Follow the instructions your treating and study doctors gave you to prepare for your MRI scan; • Tell research staff about any pre-existing conditions (health concerns) you may have; • Have a small IV line placed for contrast administration; • Receive gadolinium contrast; • Complete an MRI scan of only study-related techniques (unless otherwise indicated by your treating or study doctor) ; • Talk to your study doctor or research staff and tell them how you are feeling after your MRI scan. They will contact you between 24 – 72 hours after your MRI scan.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?

While on the study, you may be at risk for the following side effects. You should discuss these with your study and/or treating doctors. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the MRI scans are completed, but in some cases side effects can be serious, long lasting, or permanent.

Risks Associated With Intravenous (IV) Needle Placement

Likely

Minor discomfort;

- Pain in the injection site, sometimes accompanied by redness, swelling, and warmth to the area.

Less Likely

- Bruising;
- Fainting;
- Bleeding;
- Infection.

Risks Associated With Gadolinium

Approximately two percent (2%) of participants experience some side effects with the use of gadolinium; however, they are mostly mild *(nausea, headache, hives, temporary low blood pressure)*. Serious side effects are very rare and are discussed below. Recent information has suggested that the use of gadolinium may contribute to kidney disease in patients with poor kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.

Less Likely

- Headaches;
- Nausea.

Less Likely, But Serious

- Allergic-like reaction.

Very Rare, But Serious

- Nephrogenic systemic fibrosis (NSF)/Nephrogenic Fibrosing Dermopathy (NFD). NSF is a condition associated with the gadolinium contrast agent when there is severe kidney disease. Symptoms include tightening or scarring of the skin and organ failure. In some cases, it can be deadly. NSF has not been seen in patients with normal working kidneys or mild problems in kidney function. Prior to study entry and throughout the study, we will determine if your kidneys are working properly in order to help make sure the gadolinium contrast agent is safe for you.

Risks Associated With the MRI Scans

- Anxiety/stress;

- Claustrophobia;
- Discomfort.

Because of the powerful magnetic force of the MRI scanner, you may not be able to participate in the study if you have:

- 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); or
- Difficulty lying still or inability to lie on your stomach.

Notify your doctor if any of the above relate to you. Also, carefully read the information you should receive at the MRI facility about other risks.

While there are no significant risks from MRI, you may be uncomfortable due to the loud noise and/or feelings of claustrophobia during the MRI. If you experience a sensation of claustrophobia while in the magnet, the MRI will be immediately stopped. You will be excluded from the study if you have a pacemaker or other electromagnetic device, or have a vascular clip in your head. No serious biologic effects have been reported from the magnetic fields used in clinical MRI.

Risks Associated With the Endorectal Coil That May Be Used During the MRI Scan(s)

Whether an endorectal coil is or is not used during the first MRI scan depends on your treating doctor's decision (per standard practice at the treating doctor's institution and what is deemed best of you).

Likely

- Possible "warming" sensation from the endorectal coil.
- Discomfort from insertion of the rectal coil similar to that of an enema.

Less Likely, but Serious

- Rectum tear.

Rare

Another potential hazard of the examination using the endorectal coil is localized heating of the body due to the radio waves employed. Localized heating means elevation of skin temperature at the location of the endorectal coil. In the event of a heating sensation, you should notify the MR technologist immediately. However, the MR scanner and the endorectal coil have been designed to prevent this from happening, and there have been no reports of local heating in patients scanned to date.

For more information about risks and side effects, ask your study doctor.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THE STUDY?

Taking part in this study may or may not make your health better. The information from this study could help doctors better see the prostate area and better understand how treatments are working to fight cancer cells. We hope the information learned from this study will benefit other patients with prostate cancer in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?

You may choose not to take part in this study. If you choose not to participate, there will be no penalty and your treatment/medical care will not be affected.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that your personal information will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. Records of your participation on this study, your progress, and images submitted (such as the MRI scans) while you are on the study will be kept in a confidential form at *<<Institution>>* and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia. All data sent to ACRIN over the Internet will be coded so that other people cannot read it. All personal identifiers are removed and replaced with a unique identifying number.

You further understand and agree that authorized representatives of ACRIN, the Food and Drug Administration (FDA), the National Cancer Institute (NCI) and its agents and contractors, the Institutional Review Board (IRB) of *<<Institution>>* and other groups or organizations that have a role in this study may, without obtaining additional consent from you, have access to and copy both your medical and research records, including the results of your participation in this study. This access is necessary to ensure the accuracy of the findings, the completion of the study, and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner in which you cannot be identified.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Taking part in this study may lead to added costs to you or your insurance company. Please ask your study doctor about any expected added costs or insurance concerns.

You will not be responsible for the costs of any examinations or treatments that are considered part of the study and not part of standard care, such as certain sequences in the 1st MRI Scan and the entire 2nd MRI scan for the study.

However, you and/or your health insurance will be charged for any portion of your care that is considered standard of care (that is, if these expenses would have happened even if you were not in the study, such as the majority of the 1st MRI Scan) or if your insurance agrees in advance to pay. You may be responsible for any co-payments and deductibles that are standard for your insurance coverage.

You will not be responsible for the costs of any study-related examinations and treatments, including the contrast agents being used in the study. You and/or your insurance company will be charged for continuing medical care and/or hospitalization, including emergency medical care.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, *<<insert name>>*, if you feel that you have been injured because of taking part in this study or if any medical emergency, injury, or illness occurs during this study. You can tell the study doctor in person or call him/her at *<<insert telephone number>>*.

In the case of medical emergency, injury, or illness during this study, emergency medical treatment is available but will be provided at the usual charge. You and/or your insurance will be responsible for the cost of the medical care of that illness or injury. There is no financial compensation that has been set aside to compensate you in the event of injury.

WILL I BE PAID FOR BEING IN THIS STUDY?

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is your choice. You may choose not to take part in the study. If you do decided to participate, you are free to leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular treatment and medical care options now or in the future. You can still get your medical care from our institution.

During the study, we may find out more information that could be important to you. A Data and Safety Monitoring Committee (an independent group of experts) will be reviewing the data from this research throughout the study. This includes information that might cause you to change your mind about being in the study. If information becomes available from this or other studies that may affect your health, welfare, or willingness to stay in this study, we will tell you about it as soon as possible.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

This document explains your rights as a study participant. It you have any questions regarding your participation in this research study or you have any questions regarding your rights as a research participant, do not hesitate to speak with your study doctor or anyone listed below.

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, *<<insert name>>*, at *<<insert telephone number>>*.

For additional information about your health or medical emergency, you may contact: *<<Usually the name of the local hospital information is provided and with instructions to study participants to inform the ER doctor of their participation in a clinical trial.>>*

_____	_____
Name	Telephone Number

For information about this study, you may contact:

Name	Telephone Number

For questions about your rights while taking part in this study call the *<<insert name IRB contact person>>* at *<<insert name of the IRB>>* Institutional Review Board (a group of people who review the research to protect your rights) at *<<insert telephone number>>*.
<<Provide the name of a local IRB contact person.>>

Name	Telephone Number

WHERE ELSE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at: **1–800–4–CANCER (1–800–422–6237).** You may also visit the NCI's Web sites for comprehensive clinical trials information, http://cancertrials.nci.nih.gov, or the American College of Radiology Imaging Network web site, www.acrin.org.

More information on MRI scans can be found in the "Patients" section of the ACRIN web site: www.acrin.org. You or your doctor can print a description of MRI scans from this web site.

ACKNOWLEDGEMENT

When you sign this document, you are agreeing to take part in this study. This means you have read all the above information, asked questions regarding your participation, and received answers that you understand to all your questions. You also have had the opportunity to take this consent form home for review or discussion if you want to. A copy of the signed consent will be given to you.

You willingly give your consent to participate in this study.

Printed Name of Study Participant/ Legal Representative	Signature	Date

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

APPENDIX II

ACRIN 6701

SUPPLEMENTAL MATERIALS AVAILABLE ONLINE

Supplemental materials that support the conduct of the trial are available on the ACRIN Web site at the ACRIN 6701 Protocol web page (www.acrin.org/6701_protocol.aspx). Types of materials posted online include:

- Application and protocol activation documents (General Qualifying and Protocol Specific Applications, 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/6701_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 6701 Contact Personnel link on the above-mentioned Web page for a list of protocol team members at ACRIN Headquarters and their roles.