ACRIN PRELIMINARY PROTOCOL CONCEPT DEVELOPMENT

The Preliminary Protocol Concept Development form will be completed by the submitting individual in collaboration with the appropriate Disease Site Committee (DSC) Chair. The DSC Chair will forward the completed form to ACRIN Headquarters for consideration by the Steering Committee. Upon approval of the Steering Committee, the protocol trial team will be appointed to further develop the concept in the ACRIN Protocol Concept Submission document for NCI/CTEP review and approval.

This document is limited to no more than six (6) pages and each section should contain a brief description **in bullet format** (i.e. non-narrative), where it is applicable:

PRELIMINARY PROTOCOL CONCEPT DEVELOPMENT	
WORKING TITLE OF PROJECT:	Repeatability Assessment of quantitative DCE-MRI and DWI.
SUBMITTING INDIVIDUAL:	*Name of the submitting member:* Mark Rosen, MD, PhD *Specialty:* MRI *Address:* University of Penn., 3400 Spruce St., Philadelphia, PA 19104 *Phone:* 215-662-6440 *Fax:* 215-662-7263 *Email:* rosenmar@uphs.upenn.edu
INTRODUCTION/ BACKGROUND	The use of quantitative MR imaging 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. However, the extraction of reliable and reproducible quantitative features from MRI imaging has been more challenging. As more functional MR techniques such as diffusion weighted imaging (DWI) and dynamic contrast-enhanced (DCE-)MRI emerge as a means of providing physiologic information about tumor microenvironment, there is an unmet need to define whether these metrics can be reliably extracted from imaging currently performed in clinical practice, and how to best standardize imaging and post-processing/analytic techniques to provide key data. *Goals of the RSNA Quantitative Imaging Biomarker Alliance (QIBA)* The QIBA group was formed in 2008 based on funding from the RSNA and the NIBIB REF. Currently, three modality based subgroups exist: PET, CT, and MRI. The MRI subgroup is further subdivided into DCE-MRI and fMRI committees. The PIs have been members of the DCE-MRI subcommittees for the past 2-3 years, and have collaborated on the development and testing of the DCE-MRI phantom in order to better identify sources of variability in DCE-MRI based methods of T1 quantification (Guo, Reddick et al. 2009) and linear signal approximation as a surrogate of tissue R1 changes(Ashton, Raunig et al. 2008).

	Ultimately, the goal of the DCE-MRI QIBA subcommittee is to provide guidance to the imaging community of the most efficacious and reproducible methods for DCE-MRI 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, 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 QIBA DCE-MRI committee has sought to develop a clinical trial which would aid in identifying the limits of reproducibility of DCE-MRI quantitative metrics, especially in the multi-site setting critical of useful biomarker studies, is a first stage goal. 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 protocol 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. Through discussions within the QIBA DCE-MRI subcommittee, it has been agreed upon to seek a partnership with the American College of Radiology Imaging Network to facilitate the development and implementation of the test-retest DCE-MRI human study. The overall project, including the completion of the protocol, selection of participating sites, central and site regulatory approvals, and implementation is expected to last two years. Funding for an estimated 50% of the total trial budget has been obtained by the PI via the current NIBIB funding mechanism of the QIBA enterprise. This proposal, in conjunction with the RSNA Quantitative Imaging Biomarker Alliance (QIBA) will seek to complete a definitive multi-site test-retest study of DCE-MRI and DWI repeatability in humans. The target population, patients presenting for prostate MRI, will be approached for participation in this study, which will comprise two successive MRI studies on distinct days. Results from this study will gauge the repeatability of image-based extraction of quantitative metrics from DWI and DCE-MRI. *DCE-MRI in Quantification of Tumor Vascularity* Dynamic contrast-enhanced MR imaging, or DCE-MRI, has evolved as a method of quantifying the vascularity of tumors and other tissues with

	the use of rapid MR imaging during bolus administration of gadolinium. In DCE-MRI studies, the changes in tissue image intensity over time are measured through high-frame rate repeated T1W imaging before and during gadolinium administration. Due to the arbitrary scaling of tissue signal intensity in MRI, it became apparent that successful use of DCE-MRI to evaluate tumor vascular characteristics in the clinic would require 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). DCE-MRI has been used successfully a means of assessing the vascular effects of a large number 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). *Repeatabilty 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 large number of assumptions are made in order to model the expected behavior of MRI signal intensity after gadolinium introduction. In addition, 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), and early studies of DCE-MRI repeatability demonstrated relatively large coefficient of variations(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). Nevertheless, few large scale studies of DCE-MRI reproducibility in a multi-site setting have been performed. *DWI in Cancer* Diffusion weighted imaging, or 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). It 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(Koh and Collins 2007; Chandarana and Taouli 2010). Quantitative evaluation of DWI relies on the calculation of the apparent diffusion coefficient, or ADC, or tumors. Quantitative ADC analysis has demonstrated that tumors in 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 tumor ADC measurements 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) *Reproducibility of ADC mapping in DWI* 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-CNS human tissues suggest that ADC estimate accuracy ranges from 15-30%(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 (ADC or ADC^{slow}) and the intravoxel incoherent motion, or IVIC, attributed to perfusional motion of blood within tissues, also known s D* or ADC^{fast}, is being increasingly investigated as a means of expanding the range of imaging biomarkers available within the diffusion MRI exam(Chandarana, Lee et al. 2011; Klauss, Lemke et al. 2011; Sigmund, Cho et al. 2011). As such, more data on the reproducibility of multi B-value imaging is required. *DCE-MRI and DWI in prostate cancer* 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 imaging for detection of prostate cancer(Turkbey, Pinto et al. 2010). Quantitative DWI analysis has demonstrated strong correlation between tumor ADC and Gleason grade(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 7 or greater) tumor. DCE-MRI has also been used to successfully identify prostate cancer as a

	adjunct to morphologic imaging(Somford, Futterer et al. 2008), and degree of tumor vascularity strongly correlates with microvessel density and other markers of angiogenesis(Ren, Huan et al. 2008). *Rationale for the Current Patient Population for Repeatability Testing* The choice of prostate cancer patients undergoing MRI represents a consensus agreement of the PI and members of the QIBA DCE-MRI committee as the most viable target population for the test-retest study. This population provides an appropriate target in the "torso" region of the body while limiting issues of 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 there are specific imaging issues, specifically respiratory motion, common in performing DCE-MRI in typical metastatic location (e.g. lung, liver) that are not represented in the pelvis, based on organ size and location, the prostate otherwise represents an excellent surrogate for tumor imaging in the torso.
SPECIFIC HYPOTHESIS:	• Hypothesis #1: The coefficient of variation (CV) of DCE-MRI metrics K^{trans} and $IAUGC^{bn}$ as measured by median pixel values of the whole prostate, is equal to or less than 20%. • Hypothesis #2: The coefficient of variation (CV) of DWI metrics AUC^{fast}, and ADC^{slow}, as measured by median pixel values of the whole prostate, is equal to or less than 20%.

STUDY DESIGN:	• We propose to enroll 30 subjects at six participating institutions, representing each of the three major MRI vendors (Siemens, GE, Phillips). Final details of imaging protocol will be agreed upon based on input form an MR radiology representative from each of the six participating sites, as well as from additional radiologist and medical physicist participants in the trial team. • Subjects will be enrolled via outpatient radiology/MRI clinics schedules as well as from participating urology and radiation oncology clinics. • Participants will undergo two successive 3T MRI studies performed within 14 days of each other. The quantitative imaging studies (DWI, DCE-MRI will be performed without the endorectal coil. At the discretion of the participating sites, the initial MRI visit may be supplemented with endorectal coil morphologic and DW imaging.
STUDY OBJECTIVE:	• **Primary Study Objectives** • Determine the test-retest performance, as assessed by the coefficient

	of variation (CV), of the median pixel values of K^{trans} and $IAUGC^{bn}$, using the whole prostate as the target "tumor". • Determine the test-retest performance, as assessed by the coefficient of variation (CV) of the median pixel value of AUC^{fast}, and ADC^{slow}, using the whole prostate as the target "tumor". • **Secondary Study Objectives** • <u>DCE-MRI Methodology Secondary Objectives</u> • Determine whether T1-dependent or T1-independent methods for gadolinium quantification produce differing values for the CV for DCE-MRI metrics K^{trans} and $IAUGC^{bn}$. • Determine whether "high temporal resolution" arterial input function (HTR-AIF) determined via test bolus injection or standard temporal resolution (STR-AIF) determined during DCE-MRI acquisition produce differing values for the CV for DCE-MRI metrics K^{trans} and $IAUGC^{bn}$. • <u>"Tumor as Target" Secondary Objectives</u> • Determine the test-retest performance, as assessed by the coefficient of variation (CV), of the median pixel values of K^{trans} and $IAUGC^{bn}$, using the dominant tumor nodule as the target. • Determine the test-retest performance, as assessed by the coefficient of variation (CV) of the median pixel value of ADC^{fast}, and ADC^{slow}, using the dominant tumor nodule as the target. • <u>Exploratory Objectives</u> • Determine the effect of reader on the CV of DCE-MRI and DWI metrics for whole prostate and tumor nodule target lesions. • Explore the degree to which vendor selection affects the co-efficient of variation of DCE-MRI and DWI metrics. • Explore the correlation between DCE-MRI and DWI metrics for both whole prostate and dominant tumor nodule as target lesions.
ELIGIBILITY CRITERIA:	• Participants must be >18 years old. • Participants must be presenting to the radiology department of a participating institution for MRI evaluation of the prostate. • Participants must not have any contraindication for MRI, including non-compatible metallic devices or severe claustrophobia not relieved by oral anxiolytics. • Participants must have adequate renal function defined by GRF of >=60 mL/min/1.73cc. • Participants must not have received any prior external beam or brachytherapy to the prostate. • Participants must not have received any anti-androgenic therapy within 30 days prior to enrollment.

	• Participants must not have had prior hip replacement. • Participants must have the ability to understand and the willingness to sign a written informed consent form.
PRELIMINARY STATISTICAL DESIGN:	• Bland Altman statistics will be utilized to evaluate the coefficient of variation for the proposed parameters in the total cohort and in individual patient subsets as detailed above.
COMPETING PROTOCOLS:	• None
KEY REFERENCES: (20 or less)	Ashton, E., D. Raunig, et al. (2008). "Scan-rescan variability in perfusion assessment of tumors in MRI using both model and data-derived arterial input functions." J Magn Reson Imaging **28**(3): 791-796. Buckler, A. J., L. Bresolin, et al. (2011). "Quantitative imaging test approval and biomarker qualification: interrelated but distinct activities." Radiology **259**(3): 875-884. Buckler, A. J., P. D. Mozley, et al. (2010). "Volumetric CT in lung cancer: an example for the qualification of imaging as a biomarker." Acad Radiol **17**(1): 107-115. Chandarana, H., V. S. Lee, et al. (2011). "Comparison of biexponential and monoexponential model of diffusion weighted imaging in evaluation of renal lesions: preliminary experience." Invest Radiol **46**(5): 285-291. Chandarana, H. and B. Taouli (2010). "Diffusion-weighted MRI and liver metastases." Magn Reson Imaging Clin N Am **18**(3): 451-464, x. Costantini, M., P. Belli, et al. (2010). "Diffusion-weighted imaging in breast cancer: relationship between apparent diffusion coefficient and tumour aggressiveness." Clin Radiol **65**(12): 1005-1012. Dowlati, A., K. Robertson, et al. (2002). "A phase I pharmacokinetic and translational study of the novel vascular targeting agent combretastatin a-4 phosphate on a single-dose intravenous schedule in patients with advanced cancer." Cancer Res **62**(12): 3408-3416. Evelhoch, J. L. (1999). "Key factors in the acquisition of contrast kinetic data for oncology." J Magn Reson Imaging **10**(3): 254-259. Flaherty, K. T., M. A. Rosen, et al. (2008). "Pilot study of DCE-MRI to predict progression-free survival with sorafenib therapy in renal cell carcinoma." Cancer Biol Ther **7**(4): 496-501. Galbraith, S. M., R. J. Maxwell, et al. (2003). "Combretastatin A4 phosphate has tumor antivascular activity in rat and man as demonstrated by dynamic magnetic resonance imaging." J Clin Oncol **21**(15): 2831-2842. Gibbs, P., M. D. Pickles, et al. (2007). "Repeatability of echo-planar-based diffusion measurements of the human prostate at 3 T."

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	35(1): 102-107.
COMMENTS:	Preliminary budget estimates have been created with the aide of Donna Hartfiel and Dr. Mitchell Schnall. Total trial costs estimates are $350,000-$370,000. Funding from the QIBA-NIBIB contract for costs of $175,000 have recently been awarded to cover approximately 50% of the costs.

__Mark Rosen_____ _____July 14, 2011_____
Name of Person Completing Form Date

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Person Completing Form E-mail Address Phone Number

NOTE: Concepts must be submitted in electronic format by e-mail to the appropriate ACRIN parties:

- Appropriate Disease Site Committee (DSC),
- ACRIN Headquarters, or
- ACRIN Network Chair

With preliminary concept approval by the DSC, PI will present the concept to the ACRIN Steering Committee for SC approval to further development of the concept on the ACRIN Protocol Concept Submission document for NCI/CTEP review and approval.