ANGULAR INTERLEAVED PROJECTION RECONSTRUCTION WITH K-SPACE WEIGHTED IMAGE RECONSTRUCTION FOR DYNAMIC CONTRAST MRI OF CANCER THERAPY RESPONSE

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Eligibility/Registration

Patients with colorectal cancer metastatic to the liver who will be receiving FOLFOX chemotherapy with bevacizumab are eligible for this study. In addition, each patient must have a qualifying liver lesion.

Imaging

Two pre-treatment dynamic contrast-enhanced MRI studies within 2 weeks prior to the start of chemotherapy, separated by at least 48 hours.

Treatment

Participants will receive 1st cycle of chemotherapy from the treating oncologist. Chemotherapy treatment is per institution standard of care.

Imaging

Post-treatment dynamic contrast-enhanced MRI study between 8 and 14 days after 1st cycle of chemotherapy.

Observational Follow-Up

Institution standard of care chemotherapy and CT or MRI follow-up:

- Clinical assessment every 3 months (from the initiation of chemotherapy) for 24 months or until disease progression.
- CT or MRI imaging assessment every 3 months (from the initiation of chemotherapy) for 24 months or until disease progression.
Arm B

**ELIGIBILITY/REGISTRATION**

Patients with any other types of cancer metastatic to the liver

**IMAGING**

Two dynamic contrast-enhanced MRI studies performed under stable treatment conditions.*

* Refer to section 4.3 for the definition of stable treatment condition

**SPECIFIC AIMS/OBJECTIVES**

This is a phase II, multi-institution study to test the feasibility and reliability of implementing a novel MRI acquisition scheme for rapid DCE-MRI across multiple imaging platforms. The novel technique, angle-interleaved back-projection acquisition, will be developed across imaging platforms at up to five institutions in Pennsylvania. It will then be tested on a phantom system and on normal volunteers before being applied in a clinical trial of DCE-MRI to track vascular changes induced by chemotherapy containing the antiangiogenic agent, bevacizumab, in metastatic colorectal carcinoma.

The primary and secondary endpoints of this study are:

- Feasibility of protocol implementation across multiple imaging platforms.
- Test-retest repeatability for tumor $K^{\text{trans}}$ quantification in a human population of metastatic colon cancer to the liver.
- Early $K^{\text{trans}}$ changes induced by combination chemotherapy containing bevacizumab.
- Relationship between baseline tumor $K^{\text{trans}}$, early tumor $K^{\text{trans}}$ response, and clinical endpoints including PFS (progression-free survival).

**METHODS/METHODOLOGY**

The study will contain two Arms. Arms A and B will include two (2) MRI exams within a two (2)-week time period either pre-treatment (Arm A) or under stable treatment conditions (Arm B) to address reproducibility. Arm A includes a third MRI assessment between weeks 8 and 14 of initiating FOLFOX chemotherapy with bevacizumab in order to explore the ability of radial DCE-MRI to measure treatment effect. Participants in Arm A will be followed for up to two years after the initiation of chemotherapy or until disease progression. Again, Arm B contains only these two (2) MRI exams within a two-week time period under stable treatment conditions for reproducibility.

The use of projection reconstruction can provide high temporal and spatial resolution data allowing DCE-MRI to detect perfusion changes associated with tumor response. Projection reconstruction DCE-MRI (DCE-MRI) will be utilized in two populations of patients: one cohort with colorectal cancer metastatic to the liver who are to receive chemotherapy including the antiangiogenic agent bevacizumab and the other cohort those subjects with any cancer metastatic to the liver. DCE-MRI will be used to determine reproducibility of the methodology for determining kinetic parameters of tumor gadolinium entry (e.g. $K^{\text{trans}}$) (Arms A and B) and to gauge the relationship between bevacizumab-induced changes in tumor $K^{\text{trans}}$ and clinical parameters of tumor response (Arm A only).
ELIGIBILITY (see Section 5.0 for details)
All patients with colorectal cancer metastatic to the liver who will receive FOLFOX chemotherapy with bevacizumab are eligible for participation in Arm A of this study. In addition, each patient must have a measurable viable liver tumor.

Patients with any cancer metastatic to the liver who meet the eligibility criteria are eligible to participate in Arm B.

Participants must be able to sign an informed consent and agree to undergo a total of three (3) DCE-MRI scans (two separate pre-treatment and one post-treatment DCE-MRI exams) if in Arm A or two (2) DCE-MRI scans if in Arm B. All study participants—in Arms A and B—must complete two (2) separate DCE-MRI scans for reproducibility either pretreatment (Arm A) or under stable treatment conditions (Arm B) and only Arm A participants must complete one (1) additional post-treatment DCE-MRI exams. The post-treatment DCE-MRI exam in Arm A will take place between 8 and 14 days after the first cycle of chemotherapy with bevacizumab.

REQUIRED SAMPLE SIZE
A total of 60 participants will be enrolled to either Arm A or B into the study over one year period.
1.0 ABSTRACT

This protocol for human research study is conducted according to US 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.

This study will investigate the use of projection reconstruction dynamic contrast-enhanced MRI (DCE-MRI) as a surrogate marker of tumor vascularity in patients treated with the antiangiogenic agent bevacizumab. DCE-MRI is gaining popularity as a method to assess the functional response of tumors to agents targeting the VGEF pathways. DCE-MRI measurements have been proposed as a non-invasive measure of both tumor biologic activity and (in the case of antivascular therapy) early response to treatment. A number of phase I and II studies demonstrate the ability for DCE-MRI to detect perfusion changes associated with tumor biologic response to vascularly targeted agents. It has also been suggested that pre-treatment DCE-MRI might identify tumors with high intrinsic perfusion and that these tumors will be more likely to respond to antivascular-based therapies. However, the current use of DCE-MRI in clinical settings is challenging. Trade-offs between spatial coverage, time, and spatial resolution make this technique difficult to implement in human studies and may limit its reliability. The use of projection reconstruction–based acquisition can mitigate the need for these trade-offs and can simultaneously provide high temporal and spatial resolution data for DCE-MRI analysis.

This study involves the dissemination of projection reconstruction MR technology across multiple imaging centers for use in a multi-site trial of DCE-MRI in cancer patients with measurable disease before and after chemotherapy. While several kinetic models may be explored, the first-order unidirectional serum-tumor gadolinium transfer constant ($K^{\text{trans}}$) from the general kinetic model (GKM) will be used as the primary endpoint for tumor vascular assessment. In Arms A and B, two (2) scans either pre-treatment (Arm A) or under stable treatment conditions (Arm B) will be performed to determine reproducibility of the technique. Stable treatment conditions are defined as the continuation of an ongoing chemotherapy regimen that is not altered during the time between the two (2) DCE-MRI scans, and with no intervening surgical, interventional or radiation treatment between the two (2) DCE-MRI scans (see section 4.3). Only in Arm A, a follow-up DCE-MRI study will be performed after one cycle of chemotherapy to define the therapy-induced changes in $K^{\text{trans}}$. $K^{\text{trans}}$ changes will then be assessed as a predictor of clinical parameters of response, notably PFS.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Angiogenesis in Colon Cancer

One approach to the treatment of solid tumors involves therapeutic agents that inhibit vascularization of growing tumors. The evidence linking tumor growth and metastases with angiogenesis is compelling [1]. One such angiogenic factor, vascular endothelial growth factor, (VEGF) is the most potent and specific and has been identified as a crucial regulator of both normal and pathologic angiogenesis, with increased expression observed in many human tumor types [2]. In colorectal cancer, increased VEGF expression correlates with invasiveness, vascular density, metastasis, recurrence, and unfavorable prognosis [3-7]. Studies in colorectal cancer have associated the microvessel density (MVD) with progression from adenoma to cancer and from localized to metastatic disease [8-10]. High MVD confers a poorer prognosis and seems also to
determine the nature of the metastatic profile being particularly associated with hematogenous spread of the tumor. A number of studies show that MVD correlates with VEGF expression in tumors [11].

Maturation, another feature of tumor vessels, may impact tumor response to antiangiogenic agents. During developmental retinal angiogenesis, coverage of capillaries by pericytes (periendothelial mesenchymal cells characterized by expression of alpha or smooth muscle actin [SMA]) protects them from regression during the vascular remodeling that accompanies declining levels of VEGF. Pericyte coverage of vessels in murine tumors is associated with their maturation in a process resembling that seen during retinal angiogenesis. Furthermore, pericyte-covered tumor vessels in mice have been shown to be more refractory to angiogenesis inhibitor therapy involving VEGF withdrawal or using interleukin-12.

### 2.2 Bevacizumab in Colon Cancer

Bevacizumab (Avastin, Genentech, South San Francisco, CA), a recombinant humanized monoclonal antibody to VEGF, has been investigated in a number of tumor types, including colorectal cancer. Prior phase II and III studies using bevacizumab in colorectal cancer have shown it to have significant biologic activity [12].

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human VEGF (VEGF-A) with high affinity [13].

Of known proangiogenic factors, VEGF is one of the most potent and specific; it has been identified as a crucial regulator of both normal and pathological angiogenesis. VEGF is a secreted, heparin-binding protein that exists in multiple isoforms. Action of VEGF is primarily mediated through binding to the receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). The biological effects of VEGF include endothelial cell mitogenesis and migration, increased vascular permeability, induction of proteinases leading to remodeling of the extracellular matrix, and suppression of dendritic cell maturation. Neutralization of VEGF by bevacizumab has been shown to inhibit the VEGF-induced proliferation of human endothelial cells in vitro and to decrease MVD and interstitial pressure in tumor xenografts in vivo. Preliminary results from a neoadjuvant trial in rectal cancer demonstrated a decrease in blood perfusion/permeability and interstitial fluid pressure in tumors after one dose of bevacizumab [14].

In mouse models, administration of anti-VEGF monoclonal antibodies that inhibit VEGF blocks the growth of human tumor xenografts and dramatically reduces the size and number of liver tumors in a mouse xenograft model of human colon cancer metastasis [2, 15]. In addition, the combination of anti-VEGF antibody and chemotherapy in nude mice injected with human cancer xenografts has an increased antitumor effect compared with antibody or chemotherapy treatment alone.

In phase I trials, bevacizumab was generally well tolerated and did not demonstrate dose-limiting toxicity or interactions with commonly used chemotherapy regimens [16, 17]. In a phase II trial, bevacizumab at doses of 5mg/kg and 10mg/kg combined with fluorouracil and leucovorin compared with fluorouracil and leucovorin alone resulted in
higher response rates, longer median time to disease progression, and longer median survival [12]. A phase III study evaluated patients with advanced colorectal cancer randomized to receive irinotecan, 5-FU, and leucovorin (IFL) plus bevacizumab (5mg/kg) versus IFL plus placebo [18]. The median duration of overall survival, the primary end point of this study, was 20.3 months for those in the bevacizumab group and 15.6 months in the placebo group (p<.001). A subsequent phase III study (ECOG 3200) was conducted in patients with progressive metastatic colon cancer after 5-FU and irinotecan who had not received prior oxaliplatin. In this 3-arm study, patients were randomized to receive FOLFOX, bevacizumab (10mg/kg), or the combination. Patients treated with FOLFOX plus bevacizumab had an approximately 2-month improvement in PFS (7.2 vs. 4.8 months, p <0.0001) and objective survival (12.9 vs. 10.8 months, p<0.0001) and improved response rate (21.8% vs. 9.2%, p<0.0001) compared to FOLFOX monotherapy. Bevacizumab monotherapy was inferior to both other arms with respect to response rate, PFS, and overall survival.

2.3 DCE-MRI for Assessment of Tumor Vascular Response

DCE-MRI provides a non-invasive means of assessing the status of tumor microvasculature. DCE-MRI utilizes rapid T1-weighted MR imaging during bolus IV administration of small molecular weight gadolinium contrast agents to gauge tumor vascularity. Gadolinium contrast agents exert their effect by shortening the T1 relaxation time of neighboring water protons, thus leading to enhancement (brightening) of the areas of contrast accumulation on T1-weighted MR images.

During the initial passage of gadolinium through the tumor capillaries, the contrast agent will enter the tumor interstitium at a rate that is governed largely by the tumor blood flow and the endothelial permeability of the tumor vascular bed. Initial gadolinium accumulation occurs within the 1st 30-60 seconds of enhancement. This will then be followed by a 2nd phase of tumor enhancement, which will either demonstrate additional slow accumulation of contrast agent, a leveling off of contrast accumulation, or early contrast agent washout, depending on the status of the tumor vasculature.

While empiric descriptions of DCE-MRI enhancement curves can be useful [19, 20], most researchers agree that quantification of DCE-MRI enhancement curves require the conversion of image enhancement into an estimated tissue gadolinium concentration [21]. One then models the kinetics of gadolinium entry into the tumor based on measured or assumed arterial gadolinium concentrations (arterial input function, or AIF), to describe the rate of gadolinium passage from plasma into the tumor interstitium. Several different kinetic models have been proposed in the literature, though most are based on the general kinetic two-compartment model, such as defined by Kety to model physiologic gas exchange. The Tofts’ formulation of the Kety model [22, 23] (also known as the general kinetic model, or GKM) is most frequently used and allows one to derive several kinetic parameters, including the unidirectional plasma-to-gadolinium first order transfer function, K\text{trans}. In the GKM, K\text{trans} reflects a combination of vascular permeability and tumor blood flow.

DCE-MRI has been studied in numerous tumor models as a means of gauging tumor vascularity and the response of tumor vasculature to various antitumor therapies. Most recently, DCE-MRI has been proposed as a means of indirectly gauging the physiologic
activity of chemotherapy agents targeted against the tumor neovasculature. Whereas tumor shrinkage is the sine qua non of response to traditional cytotoxic chemotherapy, antitumor efficacy of antivascular or antiangiogenic targeting agent may not manifest itself early on as tumor shrinkage.

DCE-MRI has now been used as a means of documenting vascular changes in tumor vascularity following a variety of targeted chemotherapy agents [24-27]. These results suggest that early antivascular effects on tumors by targeted agents may be a means of predicting tumor response. Most recently, it has been shown that the clinical response of renal cell carcinoma and melanoma to single-agent therapy with sorafenib (measured as time to tumor progression), was heavily influenced by the initial $K_{\text{trans}}$ value of the tumor prior to initialization of therapy [28].

Therefore, there is increasing interest in the oncology community in exploring the relationship between imaging of tumor vascularity, tumor vascular response, and long-term clinical response in the setting of targeted chemotherapy.

Clinical researchers at the Hospital of the University of Pennsylvania have considerable expertise in the analysis of tumor blood flow using DCE-MRI. Previous collaborations between the Departments of Radiology and Hematology/Oncology have demonstrated the successful use of DCE-MRI to measure tumor vascularity after the administration of novel antivascular therapeutics. Previously, we have effectively demonstrated evidence of diminished tumor perfusion as measured by DCE-MRI after combretastatin A4 phosphate (CA4P) and sorafenib administration [29, 42].

2.4 Experience With Back-Projection MRI

Projection interleaved (back-projection) MRI is a method for obtaining MR imaging in which the k-space data is acquired using a non-Cartesian trajectory. Specifically, radial acquisition of data is performed at various projections to obtain a complete two-dimensional k-space data set. In three-dimensional back-projection MR image acquisition, the third (slice) dimension is obtained in the traditional rectilinear fashion. Image construction from the raw data is performed via data rebinning into the traditional Cartesian coordinates. Ramp filtering is used to compensate for the oversampling of the central region of k-space. As the k-space center is repetitively sampled during the course of the image acquisition, alternative post-processing techniques known as KWIC filtration, can be employed to allow for the acquisition of high-temporal and high-spatial resolution image sets. This technique has previously been employed successfully for dynamic contrast enhanced imaging of the breast [30, 31] and has been used for high temporal functional cardiac imaging [32].

The advantage of back-projection techniques includes the ability to obtain high temporal resolution images, albeit at lower spatial resolution. However, higher resolution imaging can be obtained through combination of the lower resolution (subaperture) data sets. Furthermore, it has been shown that the subaperture data sets can be individually corrected for motion, allowing for more robust imaging of areas of physiologic and voluntary motion during the course of dynamic imaging.
In this trial, the angle-interleaved back-projection technique will be applied to abdominal imaging to allow for large volume DCE-MRI of metastatic liver lesions in patients with advanced colorectal carcinoma (Arm A) and other cancers (Arm B).

2.5 Functional Status of Vasculature as a Predictor of Response or Disease-Free Survival

Colorectal carcinoma is a vascular tumor, and dysregulation of angiogenesis is a variable feature of the disease. Analysis of angiogenesis has in the past relied on counting the number of blood vessels in tumor. These analyses provide assessments of perfusion, but not of active angiogenesis, since they include both mature and new vessels. An assessment of new vessel formation provides a more accurate picture of active angiogenesis and is hypothesized to be a more robust predictor of the effects of angiogenesis inhibition. The functional status of the vasculature will be measured by analyzing the signal transduction mechanisms mediating the proliferative effects of VEGF through the MAP kinase pathway. ERK, of the MAPK signal transduction pathway, plays a critical role in neovascularization (35, 36, 37-39). ERK1/2 is activated in endothelial cells in response to angiogenic factors (VEGF, bFGF, and Ang-1) and is associated with proliferation of endothelial cells during neovascularization (37-39). The expression of activated ERK1/2 (p-ERK) in endothelial cells is a novel marker for identifying stimulated or activated endothelium. Ki67, a marker of endothelial proliferation, complements the pERK (or pSTAT3) measurements, and SMA, a marker of pericyte coverage, identifies mature vessels, and so also helps characterize the functional status of tumor vasculature (40). We propose the analysis of these measures (SMA, Ki67, pErk) together with MVD (anti-CD34), to determine associations with clinical outcome.

3.0 SPECIFIC AIMS/OBJECTIVES

3.1 Objective

The objective of this study is to assess reproducibility of DCE-MRI as applied to patients with metastatic liver disease from colorectal cancer or any other types of cancer. Radially acquired ("back-projection") techniques will be applied in order to decrease image acquisition time while simultaneously allowing for increases in volumetric coverage during the perfusion study. It is also expected that using subaperture back-projection images can better correct for motion, thus improving image analysis for the detection of perfusion changes associated with tumor response to therapy.

3.2 Specific Aims

3.2.1 Primary Objectives

3.2.1.1 To determine the reproducibility of DCE-MRI measures of tumor $K^{\text{trans}}$, $k_{\text{ep}}$, and $v_e$ for colorectal metastases to the liver (Arm A) and any cancer metastatic to the liver (Arm B), using projection interleaved back-projection DCE-MRI techniques.

3.2.1.2 To determine the alteration in tumor vascularity (assessed by percentage change in tumor $K^{\text{trans}}$) in Arm A participants with metastatic colorectal cancer to the liver after one cycle of chemotherapy including bevacizumab compared to baseline $K^{\text{trans}}$ value.

3.2.2 Secondary Objectives

3.2.2.1 To determine the relationship between initial tumor vascularity (as assessed by absolute
tumor $K^{\text{trans}}$ and change in tumor vascularity (as assessed by percentage change in tumor $K^{\text{trans}}$ following one cycle of chemotherapy) and PFS in participants in Arm A (receiving FOLFOX chemotherapy plus bevacizumab).

3.2.2.2 To evaluate the perfusional difference between the dominant tumor and the global tumor burden (Arms A and B).

3.2.2.3 To evaluate the feasibility of exporting back-projection DCE-MRI imaging across multiple MRI scanner vendor platforms for use in a multi-site chemotherapy trial.

3.2.2.4 To determine the functional status as a predictor of response or disease-free survival in participants in Arm A.

4.0 STUDY OVERVIEW

This is a multi-center study that anticipates accrual of 60 participants over a one year period. The study will contain two Arms. Arms A and B will include two (2) DCE-MRI exams within a two (2)-week time period either pre-treatment (Arm A) or under stable treatment conditions (Arm B) to address reproducibility. Arm A includes a third DCE-MRI assessment between weeks 8 and 14 of initiating FOLFOX chemotherapy with bevacizumab in order to explore the ability of radial DCE-MRI to measure treatment effect. Participants in Arm A will be followed for up to two (2) years after the initiation of chemotherapy or until disease progression.

4.1 Arm A:

Participants in Arm A will have two (2) pre-treatment DCE-MRI scans separated by at least 48 hours, but no more than 2 weeks of each other, and a third DCE-MRI assessment between weeks 8 and 14 of initiating FOLFOX chemotherapy with bevacizumab. The third scan is completed to explore the ability of radial DCE-MRI to measure treatment effect. Participants in Arm A will be followed for up to two (2) years after the initiation of chemotherapy or until disease progression.

4.1.1 Definition of Treatment Cycles and Follow-Up Timelines

Per the eligibility criteria of the protocol, eligible participants enrolled to Arm A in this imaging study will be treated with FOLFOX in combination with bevacizumab. FOLFOX chemotherapy plus bevacizumab is considered the standard first-line therapy for metastatic colorectal cancer. The dose for bevacizumab will be standard of care per institution requirements.

For this study, the chemotherapy cycle includes a single dose of FOLFOX and bevacizumab, repeated every 2 weeks. Chemotherapy treatments will be standard of care for each participant. It is, however, possible that evolving combination therapies will incorporate a different timing. The actual timing of a chemotherapy cycle will be defined by the treating oncologist for each participant. Follow-up imaging to define tumor response by RECIST criteria will similarly depend on the cycle timing and other clinical parameters (See Appendix IV). It is presumed that routine follow-up imaging will take place approximately once every 3-4 cycles (i.e. every 6-8 weeks).
4.2 **Arm B**: Arm B will include only two (2) DCE-MRI exams separated by least 48 hours, but no more than 2 weeks of each other under stable treatment conditions to address reproducibility.

4.3 **Definition of Stable Treatment Conditions**

4.3.1 Participants are defined as being under stable treatment conditions prior to enrollment if they meet one of the following conditions at entry:

1) Have not received any medical, surgical, interventional, or radiation treatment for their cancer over the past 4 weeks prior to registration, and are not anticipated to receive any new therapy prior to completion of the two DCE-MRI studies.

OR

2) Have not received any surgical, interventional, or radiation treatment for their cancer over the past 4 weeks prior to registration and are currently receiving a non-experimental chemotherapy regimen that was initiated greater than 4 weeks before enrollment, does not include any biologically targeted (e.g. anti-angiogenic, anti-EGFR, etc.) agents, and are not anticipated to receive any new therapy (ies) prior to completion of the two DCE-MRI studies.

4.3.2 Participants are defined as having been under stable treatment during the conduct of the study (i.e. from the time of enrollment until completion of the second DCE-MRI study) if 1) they met the definition of stable treatment conditions above prior to enrollment, 2) have not undergone any surgical, interventional, or radiation treatment to the liver since enrollment, and 3) have not received any new chemotherapy agent since enrollment.

During the conduct of the study, changes in dosage or scheduling or discontinuation of an existing chemotherapy regimen will not constitute a deviation from stable treatment conditions, and will be allowed if deemed medically necessary by the participant’s treating physician.

5.0 **PARTICIPANT SELECTION**

5.1 **Arm A: Inclusion Criteria**

5.1.1 Participants must be \( \geq 18 \) years old;

5.1.2 Participants must have an ECOG performance status of 0-1;

5.1.3 Participants must not be pregnant or breastfeeding;

5.1.4 Participants must have prior histological documentation of adenocarcinoma of the colon or rectum;

5.1.5 Participants must be commencing chemotherapy with FOLFOX plus bevacizumab;
5.1.6 Participants must not have had prior exposure to bevacizumab. Prior systemic chemotherapy with other agents is allowed. The last dose of systemic chemotherapy must have been > 3 months prior to study entry;

5.1.7 Participants with prior radiotherapy or other prior local therapy to the liver (radioablation therapy, chemoembolic therapy) are acceptable. They must be at least 4 weeks past the last administration of such therapy;

5.1.8 Participants must be at least 4 weeks past any major surgery, including surgery to the liver;

5.1.9 Participants with prior malignancies other than colon cancer are allowed, provided they have been treated with curative intent, and have no evidence of recurrence of that malignancy;

5.1.10 Participants must have a life expectancy of greater than 3 months;

5.1.11 Participants must have the ability to understand and the willingness to sign a written informed consent form.

5.2 Arm B: Inclusion Criteria

5.2.1 Participants must be ≥18 years old;

5.2.2 Participants must have an ECOG performance status of 0-1;

5.2.3 Participants must not be pregnant or breastfeeding;

5.2.4 Participants must have prior histological documentation of any types of cancer with metastasis to the liver (see Imaging Criteria below);

5.2.5 Participants must be projected to be within a stable treatment condition prior to and between scans (see section 4.3 for definition of stable treatment condition);

5.2.6 Participants must be at least 4 weeks past any major surgery, including surgery to the liver;

5.2.7 Participants must have a life expectancy of greater than 3 months;

5.2.8 Participants must have the ability to understand and the willingness to sign a written informed consent form.

5.3 Arms A and B: Pre-Registration Imaging Inclusion Criteria

5.3.1 Participants must have at least one hepatic lesion greater than or equal to 3 cm in maximal diameter on cross sectional imaging study (CT or MRI) performed within 4 weeks prior to study enrollment;

5.3.2 Participants must have at least one qualifying liver lesion (i.e. one greater than or equal to 3 cm) that has been confirmed metastatic cancer on one of the following criteria:

   o Histologic (FNA or core biopsy) proof of malignancy compatible with metastasis from a colorectal or other primary carcinoma;

   OR
Demonstration of imaging features of tumor metastasis to the liver, including at least one of the following:

a) evidence of heterogeneous enhancement or central tumor necrosis by CT or MRI;

b) previously demonstrated interval enlargement of the lesion by >25% in the longest diameter;

c) PET image demonstrating metabolic activity characteristic of malignancy (FDG uptake greater than that of background liver).

5.3.3 For participants who have undergone local hepatic surgical, radiation, ablative, or embolic therapy, the date of qualifying imaging study(ies) or qualifying biopsy must be at least 30 days after the last instance of such local therapy. Furthermore, cross-sectional imaging performed at least 30 days after such local therapy must demonstrate an area of residual viable tumor (as judged by enhancing tissue following contrast administration) with longest diameter ≥ 3cm in at least one cross-sectional axis.

5.4 Arms A and B (Unless Otherwise Indicated): Exclusion Criteria

5.4.1 Patients with contraindication to MRI, including:

5.4.1.1 Contraindicated metallic device, including pacemaker, non-MRI compatible aneurysm clip, other non-MRI compatible mechanical and/or electrical device, or metallic fragments;

5.4.1.2 Patients with severe claustrophobia (patients with milder forms of claustrophobia that can be successfully allayed with oral anxiolytic therapy are allowed);

5.4.2 Patients with contraindication to gadolinium, including:

5.4.2.1 Hypersensitivity to gadolinium-containing MR contrast agents;

5.4.2.2 Severe impaired renal function with estimated glomerular filtration rate <30 mL/min/1.73 m² and/or on dialysis;

5.4.3 Patients with severely compromised pulmonary, cardiovascular, or mental status. Patients must not have severe congestive heart failure (defined as New York Heart Association Class II or greater);

5.4.4 For Arm A only: Any other major medical illness that, in the investigator’s opinion, would: (1) prevent administration or completion of institution's standard of care FOLFOX/bevacizumab therapy; (2) prevent administration or completion of protocol-specified imaging; and/or (3) interfere with follow-up.

5.5 Recruitment Process and Tools

One or more oncologists associated with each imaging site will be approached by the radiology PI or his/her ACRIN site radiology research associate (ACRIN site RA) to describe the study. At each participating site, at least one oncologist treating patients with colorectal cancer metastatic to the liver or any other types of cancer metastatic to the liver must agree to serve as a co-investigator on the study. However, all oncologists directly or indirectly affiliated with the participating institution may serve as a source of participants for this trial in either Arm A or B. Patients with any types of cancer with metastases to the liver are eligible for only Arm B. For patients in Arm A, trial
participation should then be discussed with the oncologist (coordinated by the ACRIN site RA) prior to the initiation of the new chemotherapy regime. The site radiologist must confirm that the potential participant meets the eligibility criteria for either Arm A or B.

6.0 SITE SELECTION

6.1 Institution Requirements

Due to the funding sources for this study, only sites within the Commonwealth of Pennsylvania are eligible to participate. Furthermore, sites must have radiologic expertise in abdominal MRI applications and must be willing to participate with the protocol development team to apply the experimental back-projection technology at their institution.

6.1.1 Equipment Requirement

The 1.5T scanner must be from one of the following manufacturers: Siemens, General Electric, or Philips. Minimum gradient strengths of 33 mT/m and slew rates of 120 T/m/s are required. The same scanner must be used throughout the study at each participating institution.

6.1.2 Site must have completed and sent in the ACRIN general and protocol specific applications for approval.

6.1.3 Sites must complete phantom and human test subject imaging prior to participant enrollment. These images must be approved by the central review site prior to initiating study accrual.

6.2 Regulatory Documents

All institutions must have study-specific Institutional Review Board (IRB) approval for the protocol and informed consent form. (The informed consent form is included in this protocol as Appendix I.) 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 at the institution. In addition, sites must provide a copy of the most current OHRP Federal Wide Assurance (FWA). Copies of the IRB approval letter, the IRB approved, institutional study-specific consent form, and the FWA must be on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: Protocol Development and Regulatory Compliance [PDRC] Department) prior to registering the first participant.

7.0 PRE-STUDY QUALIFICATION

7.1 Site Approval Process

7.1.2 Implementation of Angle-Interleaved Back-Projection Sequence

Primary development of sequences will take place at the Hospital of the University of Pennsylvania (HUP) using a Siemens and GE scanner and at Thomas Jefferson University using a Phillips scanner. These developmental sites will write sequences for these scanners based on a programming code developed at HUP.
Testing of the sequence during its development will be on a T1 phantom and subsequently on two (2) test subjects. Following completion of the development, the remaining non-development site(s) will validate that the sequence is running properly on their MR scanner using phantom tests and scans of two (2) test subjects.

### 7.2 Phantom Imaging

#### 7.2.1 Phantom

Gadolinium phantoms will be made available to the participating sites. Each site will be supplied a DCE-MRI phantom containing a series of 50 mL conical tube containing ~40 mL each of a gadolinium/saline dilution, all within a styrofoam tube rack. The gadolinium dilutions will be as follows:

<table>
<thead>
<tr>
<th>Gadolinium mM</th>
<th>est. R1 (s-1)</th>
<th>est. T1 (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.88</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>1.26</td>
</tr>
<tr>
<td>4</td>
<td>0.3</td>
<td>1.64</td>
</tr>
<tr>
<td>5</td>
<td>0.4</td>
<td>2.02</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>2.4</td>
</tr>
<tr>
<td>7</td>
<td>0.75</td>
<td>3.35</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>4.3</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>6.2</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>8.1</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>11.9</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>15.7</td>
</tr>
<tr>
<td>13</td>
<td>5</td>
<td>19.5</td>
</tr>
<tr>
<td>14</td>
<td>6</td>
<td>23.3</td>
</tr>
<tr>
<td>15</td>
<td>7.5</td>
<td>29</td>
</tr>
<tr>
<td>16</td>
<td>corn oil</td>
<td>5</td>
</tr>
</tbody>
</table>

#### 7.2.2 Phantom Set-Up

The DCE-MRI phantom should be placed in the middle of the table. Larger coil loading phantoms should also be placed to ensure adequate coil loading. See the figures located in Appendix VI showing the demonstration of two different DCE-MRI and coil loading phantom arrangements.

The institutional routine for surface array coil abdominal imaging should be used with the phantom. This would typically involve posterior and anterior surface coil combinations or anterior surface with built-in spine coil. Alternative coil combination may be used as per institutional routine. The geometric placement of coils and phantoms is shown in Appendix VI.

#### 7.2.3 Phantom Imaging Parameters

Each site will image the phantom prior to participant enrollment. Phantom imaging must also be performed subsequent to any hardware or software upgrade/alterations. Localizer sequences should be performed initially. A coronal three-dimensional scan of the
phantom should be prescribed as described below. The phantom should be scanned first with a conventional (Cartesian) 3D sequence per Appendix III.

7.3 Submission and Approval of Phantom Images
Phantom images from each site will be assessed for overall image quality. In addition, image signal to noise and contrast to noise ratios will be assessed. SNR and CNR for back-projection imaging must come within 20% of those values obtained through rectilinear imaging to be acceptable. Each site must submit and receive approval of phantom imaging before proceeding to imaging of test subjects.

7.3.1 Human Test Subject Images
Sites must submit one (1) qualifying image set from human subjects prior to enrollment of the first participant in the study. A qualifying image set will include three-dimensional spoiled gradient echo scan of the liver in the axial plane performed with rectilinear data acquisition. Imaging should be performed during end expiratory breath-holding per Appendix III.

7.3.2 Source of Test Imaging
Test imaging will be performed by each site on one (1) human test subject. Sites may use normal volunteers without liver lesions as test subjects for DCE-MRI imaging. Gadolinium is not required for imaging of test subjects. Alternatively, test image submission may be performed during routine clinical abdominal MRI study, if such additional non-clinical imaging is allowed by the institutional guidelines. In such a setting, it is suggested that the test imaging be performed at the end of the routine clinical study, following dynamic contrast imaging of the liver. However, pre-gadolinium imaging is also acceptable in these cases.

7.3.3 Approval of Test Image Submission
Test subject imaging will be evaluated at the central image review site. Test subject imaging will be evaluated similarly to that of phantom imaging. SNR liver and CNR liver versus muscle will be evaluated. For back-projection imaging, these ratios must not be less than 20% of those for rectilinear imaging.

8.0 STUDY PROCEDURES
8.1 Participant Qualification (Arms A and B)
In order to assess the patient’s eligibility, the site radiologist must confirm that the potential participant meets the eligibility criteria specific to Arm A or Arm B in conjunction with the site oncologist (coordinated by the ACRIN site RA). Medical eligibility will be determined as detailed in the inclusion and exclusion criteria section of the protocol (see Section 5.0). This will require thorough review of prior imaging studies. If local therapy to the liver has previously been performed, the site radiologist should also confirm that imaging qualification has taken place subsequent to such therapy. Potential participants for Arm A must be scheduled by the site oncologist to receive FOLFOX chemotherapy plus bevacizumab treatment.
8.2 Treatment Plan (Arm A only)

Chemotherapy treatment will be standard of care for each participant in Arm A. Arm A participants will receive FOLFOX chemotherapy plus bevacizumab. Arm A participants must be treated by an oncologist at or affiliated with a participating DCE-MRI institution in Pennsylvania. A sample FOLFOX/bevacizumab regimen (mFOLFOX6) is listed below; additional options for FOLFOX regimens are acceptable and are listed in Appendix VII.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Treatment Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>85mg/m²</td>
<td>IV infusion over 2 hours</td>
<td>Day 1</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>400mg/m²</td>
<td>IV infusion over 2 hours</td>
<td>Day 1</td>
</tr>
<tr>
<td>5-fluorouracil (5-FU)</td>
<td>400mg/m²</td>
<td>IV bolus immediately following leucovorin</td>
<td>Day 1</td>
</tr>
<tr>
<td>5-fluorouracil (5-FU)</td>
<td>2,400mg/m²</td>
<td>IV continuous infusion over 46 hours immediately following bolus injection</td>
<td>Days 1-2</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Standard of care per institutional requirements</td>
<td>IV continuous infusion over 90 minutes</td>
<td>Day 1</td>
</tr>
</tbody>
</table>

NOTE: Oxaliplatin and leucovorin can be administered simultaneously using Y-line tubing provided that the leucovorin has been diluted with 5% dextrose in water and NOT 0.9% sodium chloride because of the incompatibility of oxaliplatin and saline.

Participants will receive 2nd and continuous cycles of therapy from their treating oncologist, per standard of care.

8.3 DCE-MRI Imaging Plan

Arm A:

For Arm A, participants will receive two (2) DCE-MRI scans, separated by at least 48 hours but no more than two (2) weeks between the scans. These two (2) scans must be performed prior to initiation of chemotherapy. These two (2) pre-treatment scans are intended to evaluate the reproducibility of the DCE-MRI measures in the absence of systemic chemotherapy. Participants will then undergo a third (3rd) DCE-MRI scan between weeks 8 and 14 after the initial cycle of chemotherapy to assess for therapy-induced changes in tumor vascularity. The same scanner must be used at each study visit.

Arm A participants will continue chemotherapy per standard of care with their oncologist and will not receive any additional study-related imaging after the 3rd DCE-MRI exam. However, participants will remain on study for up to 2 years, or until tumor progression, in order to obtain clinical and morphologic imaging follow-up parameters.
Arm B:
Participants in Arm B will undergo two (2) DCE-MRI scans separated by at least 48 hours but no more than two (2) weeks between the scans during stable treatment conditions (see section 4.3 for details).

8.4 DCE-MRI Imaging Procedures
Imaging will be performed according to institutional routine procedures for performing abdominal MRI. In general, it is expected that a multi-coil torso array will be used for signal reception and that the body coil will be used for signal transmission. Other coil arrangements are acceptable if they comply with the individual institution routine for abdominal MRI.

After participant positioning, the following sequences will run through the entire liver prior to performing the DCE-MRI study. For more information, refer to the detailed parameter chart in Appendix III.

8.4.1 Localizer sequences, per institutional routine.

8.4.2 Axial T1 weighted sequences through liver per institutional routine dual echo (in-phase and opposed-phase) spoiled gradient echo series recommended.

8.4.3 Axial T2 weighted sequences through the liver per institutional routine. Acceptable sequences include single-shot FSE (HASTE), FSE, or STIR sequences. It is recommended, but not required, that at least one long echo time sequence be run in addition to standard T2 weighted sequences.

8.4.4 A T1-mapping series. This will consist of five distinct axial three-dimensional spoiled gradient echo series, with back-projection technique. Detailed imaging parameters are available in Appendix III.

8.4.5 A DCE-MRI series with back-projection technique using the high flip angle. The DCE-MRI series will use identical imaging parameters of the T1-mapping series. The DCE-MRI study will be performed during quiet respiration. Imaging will be run continually for 5 to 8 minutes. Contrast injection should begin after 30 to 60 seconds of imaging.

8.4.6 Two-dimensional axial T1 weighted spoiled gradient echo series through the liver with fat suppression.

If additional pre-gadolinium or delayed post-gadolinium imaging is routinely obtained by the imaging institution or is deemed necessary to document disease sites/response, such imaging may be performed. However, the DCE-MRI protocol must be performed during the bolus administration of IV contrast.

8.5 IV Gadolinium Injection
Participant should have peripheral IV access secured ahead of time. The site and gauge of the IV access must be noted. Whenever possible, the IV access conditions should be replicated for each DCE-MRI study. For follow-up studies, the MR nurse/technologist should consult the earlier DCE-MRI study notes to replicate IV conditions. When IV
access cannot be obtained, the use of centrally placed IV access (port) is acceptable if the participant has it placed for clinical reasons. The radiologist must ascertain whether the port is graded for use with a power injector. If not, then hand injection should be used as described below.

One of three FDA-approved small molecular weight gadolinium contrast agent, Omniscan, ProHance, or Magnevist, may be used for this study. MultiHance, although approved for use in MRI, may not be employed for this study. This is due to the markedly different T1 relaxivity properties of this agent relative to the other gadolinium contrast agents, as well as the propensity for hepatic excretion.

Gadolinium dose of 0.1 mmol/kg should be used. A maximum dose of 20cc is acceptable for participants weighing greater than 100 kg (220 lbs). Gadolinium will be administered by power injector (unless contraindicated for central venous access) at a rate of 1.0 cc/sec, followed by a 20 cc saline flush for 1.0 cc/sec. If hand injection is required, the rate of contrast and saline flush should approximate 1 cc/sec.

8.6 Study Procedures
Eligible participants will be enrolled in Arm A or B depending on their cancer diagnosis. Arm B will include participants with any cancer metastatic to the liver. Arm A will include participants with colorectal cancer metastatic to the liver.

Arm A participants will undergo two (2) pre-treatment DCE-MRI scans separated by at least 48 hours but no more than 2 weeks of each other to address reproducibility. A third DCE-MRI scan will be performed between weeks 8 and 14 of initiating FOLFOX chemotherapy with bevacizumab in order to explore the ability of radial DCE-MRI to measure treatment effect. Participants in Arm A will be followed for up to two (2) years after the initiation of chemotherapy or until disease progression.

Pathology specimens will be submitted for Arm A participants if the participant agreed to pathologic analysis during the informed consent process (Sec. 10.0)

Arm B will participants will undergo two (2) DCE-MRI exams separated by least 48 hours but no more than 2 weeks of each other under stable treatment conditions to address reproducibility.

8.6.1 ARM A VISIT SCHEDULE
8.6.1.1 Visit 1: Registration Visit
- Obtain a signed informed consent form;
- Obtain a medical history to determine eligibility. If confirmation of recent negative pregnancy test and normal creatinine levels are not available in the medical history, standard-of-care pregnancy test and blood work to determine creatinine clearance will be necessary before DCE-MRI procedures;
- Register the eligible study participant;
- Forward pre-enrollment CT or MRI images to ACRIN.
Complete ACRIN CRF documenting pre-enrollment imaging assessment and clinical history and submit via the ACRIN web site. The corresponding report is mailed or faxed to ACRIN. A copy of the source documents should be filed in the study chart.

8.6.1.2 Visit 2: Within 2 Weeks Prior to the Start of Cycle 1 of Chemotherapy

- Confirm participant pregnancy status per institutional standard of care prior to DCE-MRI;
- Administer one of three FDA-approved small molecular weight gadolinium contrast agents: Omniscan, ProHance, or Magnevist;
- Perform 1st pre-treatment dynamic contrast enhanced DCE-MRI study, using the same scanner from the qualification cases;
- Assess for any adverse events relating to the DCE-MRI imaging component of the trial;
- Obtain the tumor sample from the original diagnostic biopsy, if the participant consents (Refer to section 10.0 for pathology submission);
- Forward the DCE-MRI images to ACRIN.

Complete the ACRIN CRF documenting the DCE-MRI procedure and method of gadolinium injection, and submit via the ACRIN web site. The corresponding report is mailed or faxed to ACRIN. A copy of the source documents should be filed in the study chart.

8.6.1.3 Visit 3: At Least 48 Hours but No More Than 2 Weeks After Visit 2

- Confirm participant pregnancy status per institutional standard of care prior to DCE-MRI;
- Administer one of three FDA-approved small molecular weight gadolinium contrast agents: Omniscan, ProHance, or Magnevist (whenever possible, the IV access conditions should be replicated for each DCE-MRI study; see section 8.5);
- Perform 2nd pre-treatment DCE-MRI study, using the same scanner from the participant’s Visit 2;
- Assess for any adverse events relating to the DCE-MRI imaging component of the trial;
- After obtaining the 2nd pre-treatment DCE-MRI scan, participants will receive per institutional standard of care, one cycle of chemotherapy from their treating oncologist;
- Forward the DCE-MRI images to ACRIN.

Complete the ACRIN CRF documenting the DCE-MRI procedure and method of gadolinium injection, and submit via the ACRIN web site. The corresponding report is mailed or faxed to ACRIN. A copy of the source documents should be filed in the study chart.
8.6.1.4 Visit 4: Between 8-14 Days After Cycle 1 of Chemotherapy

- Confirm participant pregnancy status per institutional standard of care prior to DCE-MRI;
- Administer one of three FDA-approved small molecular weight gadolinium contrast agents: Omniscan, ProHance, or Magnevist (whenever possible, the IV access conditions should be replicated for each DCE-MRI study; see section 8.5);
- Perform post-treatment DCE-MRI study after completion of cycle 1 of chemotherapy but before the start of the 2nd cycle of chemotherapy, using the same scanner from the participant’s Visits 2 & 3;
- Assess for any adverse events relating to the DCE-MRI imaging component of the trial;
- Forward DCE-MRI images to ACRIN.

Complete the ACRIN CRF documenting the DCE-MRI procedure and method of gadolinium injection, and submit via the ACRIN web site. The corresponding report is mailed or faxed to ACRIN. A copy of the source documents should be filed in the participant’s study chart.

8.6.1.5 Study Follow-Up: Clinical Response

All participants will be treated and followed clinically per the institution’s standard of care or per the recommendations of the participant’s treating physician. Observational clinical follow-up will be assessed every 3 months for 2 years or until disease progression.

- Perform diagnostic follow-up cross-sectional imaging visits per the institution’s standard of care every 6 to 8 weeks from the initiation of chemotherapy.

**NOTE:** ACRIN will collect the diagnostic cross-sectional images, reports, and ACRIN CRFs every 3 months (from the initiation of chemotherapy) for 2 years or until disease progression. A copy of the source documents should be filed in the participant’s study chart.

- The ACRIN site RA will contact the participant’s treating physician every 3 months (from the initiation of chemotherapy) for 2 years, or until disease progression for information pertaining to clinical status, systemic and local therapies to the liver, and disease progression.

**NOTE:** ACRIN will collect information concerning the participant’s clinical status; systemic and local therapies to the liver; and disease progression on ACRIN CRFs every 3 months (after the initiation of chemotherapy) for 2 years or until disease progression. A copy of the source documents should be filed in the participant’s study chart.

8.6.2 ARM B VISIT SCHEDULE

8.6.2.1 Visit 1: Registration Visit
- Obtain a signed informed consent form;
Obtain a medical history to determine eligibility, including treatment status.

If confirmation of recent negative pregnancy test and normal creatinine levels are not available in the medical history, standard-of-care pregnancy test and blood work to determine creatinine clearance will be necessary before DCE-MRI procedure;

Register the eligible study participant;

Forward pre-enrollment CT or MRI images to ACRIN.

Register the eligible study participant;

Forward pre-enrollment CT or MRI images to ACRIN.

Complete ACRIN CRFs documenting pre-enrollment imaging assessment and clinical history, including treatment status then submit via the ACRIN web site. The corresponding report is mailed or faxed to ACRIN. A copy of the source documents should be filed in the study chart.

8.6.2.1 Visit 2: Within 2 Weeks after Visit 1: Registration Visit

Confirm participant pregnancy status per institutional standard of care prior to DCE-MRI;

Obtain treatment status to ensure stable treatment condition;

Administer one of three FDA-approved small molecular weight gadolinium contrast agents: Omniscan, ProHance, or Magnevist;

Perform 1st DCE-MRI study, using the same scanner from the qualification cases;

Assess for any adverse events relating to the DCE-MRI component of the trial.

Forward the DCE-MRI images to ACRIN.

Complete the ACRIN CRF documenting the DCE-MRI procedure and method of gadolinium injection, including treatment status then submit via the ACRIN web site. The corresponding report is mailed or faxed to ACRIN. A copy of the source documents should be filed in the study chart.

NOTE: Should a registered participant be unable to begin the DCE-MRI scans within 2 weeks after Visit 1: Registration Visit, they will be considered a screen failure and will need to be re-registered into the system when eligibility and stability of condition are reconfirmed.

8.6.2.2 Visit 3: At Least 48 Hours but No More Than 2 Weeks After Visit 2

Confirm participant pregnancy status per institutional standard of care prior to DCE-MRI;

Assess for treatment status to ensure stable treatment conditions;

Administer one of three FDA-approved small molecular weight gadolinium contrast agents: Omniscan, ProHance, or Magnevist (whenever possible, the IV access conditions should be replicated for each DCE-MRI study; see section 8.5);

Perform 2nd DCE-MRI study, using the same scanner from the participant’s Visit 2;
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- Assess for any adverse events relating to the DCE-MRI component of the trial;
- Forward the DCE-MRI images to ACRIN.

Complete the ACRIN CRFs documenting the DCE-MRI procedure and method of gadolinium injection, including treatment status then submit via the ACRIN web site. The corresponding imaging report is mailed or faxed to ACRIN. A copy of the source documents should be filed in the study chart.
### 8.7 Study Procedures Timetables

#### 8.7.1 Arm A Visit Schedule

<table>
<thead>
<tr>
<th>Study Procedure</th>
<th>Visit 1: Registration visit</th>
<th>Visit 2: Within 2 weeks prior to the start of cycle 1 of chemotherapy</th>
<th>Visit 3: At least 48 hours but no more that 2 weeks after Visit 2</th>
<th>Visit 4: Between 8-14 days after cycle 1 of chemotherapy</th>
<th>Study Follow-up Visits&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signed Informed Consent Form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History, Including Confirmation of Safe Creatinine Levels</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirm Negative Pregnancy Status</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ACRIN Web Registration</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer Gadolinium</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>DCE-MRI Scan</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCE-MRI Imaging Component Adverse Event Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard of Care Chemotherapy</td>
<td>X&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>X&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Standard of Care: Clinical/ Radiologic Assessment: Vital Status &amp; Tumor Response or Tumor Progression</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>1</sup> After obtaining 2<sup>nd</sup> pre-treatment DCE-MRI scan, participants should receive their standard of care cycle 1 of chemotherapy.

<sup>2</sup> After obtaining the post-treatment DCE-MRI scan, participant should receive their standard of care cycle 2 of chemotherapy.

<sup>3</sup> Obtain participant’s standard of care clinical and imaging assessments for every 3 months, up to 24 months after the initiation of chemotherapy or until disease progression.
### 8.7.2 Arm B Visit Schedule

<table>
<thead>
<tr>
<th>Study Procedure</th>
<th>Visit 1: Registration Visit</th>
<th>Visit 2: Within 2 weeks After Visit 1: Registration Visit</th>
<th>Visit 3: At least 48 hours but no more that 2 weeks after Visit 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signed Informed Consent Form</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History, Including Confirmation of Safe Creatinine Levels</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirm Negative Pregnancy Status</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ACRIN Web Registration</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess for treatment status to confirm stable treatment condition</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Administer Gadolinium</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>DCE-MRI Scan</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>DCE-MRI Imaging Component Adverse Event Assessment</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
9.0 DCE-MRI IMAGING ANALYSIS

DCE-MRI analysis will take place at a central review site at the University of Pennsylvania. Raw data from the back-projection scans will be stripped of participant identifiers and replaced with a study specific ID# and time point at the imaging centers. This will be sent to ACRIN electronically in the native format of the specific scanner used at each institution. All additional imaging will be sent to ACRIN electronically in DICOM format with the participant identifiers anonymized.

Full and subaperture DCE-MRI images will be reconstructed off-line. Subaperture time resolution will be approximately 5 seconds. Motion correction of the liver will be performed on the subaperture images to minimize interscan displacement of the liver. The transformation matrix of each subaperture image will be recorded in order to replicate the motion correction algorithm. The reconstructed back-projection images will be converted to DICOM format and transmitted back ACRIN for review.

Each visible liver tumor will be manually outlined by the central radiologist on the pre-contrast imaging. The largest viable tumor on the 1st pre-chemotherapy study will be labeled as the “dominant” tumor. All other tumors with at least one dimension > 3 cm will be enumerated as separate lesions. Pixels belonging to all such tumors will be used to define the global tumor burden.

T1-maps will be computed from the multi-flip angle data. This T1 information will be used to compute estimated tumor gadolinium concentrations at each time point of the DCE-MRI study, using the baseline intensity measures. ROI of the aorta will be drawn to provide a patient-specific arterial input function (AIF).

The tumor gadolinium data will be fit to the two-compartment GKM model. $K_{\text{trans}}$, $k_{\text{ep}}$, and $v_\text{e}$ will be computed at each pixel within the identified tumor(s). Goodness of fit criteria will be implemented, including:

1. $v_\text{e} < 1.0$
2. $K_{\text{trans}} > 0.0$, $< 3.0 \text{ min}^{-1}$
3. Goodness of fit ($R^2 > 0.8$)

For the dominant tumor, median DCE-MRI parameters will be computed for all pixels with acceptable kinetic fits. The global median tumor DCE-MRI parameters will also be computed from the global tumor burden as defined above (see section 19.0 for details).

10.0 PATHOLOGY ANALYSIS: Optional for Study Participants in Arm A Only

Analysis of MVD will be by immunohistochemical (IHC) staining of tissues for CD34 and CD105, followed by counting by accepted methodology (43). Activation status of endothelial cells will be quantified using an automated IHC methodology, currently in beta-testing at the University of Pennsylvania. Simultaneous multicolor analysis of pERK, SMA, Ki-67, and other relevant antigens will be performed using validated assays. Output from the automated IHC methodology will consist of two continuous scores: intensity and percent positivity. Cutpoints that best distinguish favorable and unfavorable disease-free survival will be elicited for each parameter using recursive partitioning. These cutpoints will then be used to explore differences
in disease-free survival within treatment arms. Permutation tests will be used to assign statistical significance to the differences. The potential utility of a score combining intensity and percent positivity will also be explored. If adequate samples are available, test and validation datasets will be used to evaluate the robustness of the cutpoints and markers.

In animal models of colorectal cancer, determinants of response to antiangiogenic therapy include susceptibility of the cells to hypoxia-induced apoptosis. Ongoing ECOG studies in other diseases are investigating the participation of apoptotic markers, especially those related to hypoxia-mediated apoptosis in disease response. Markers relevant to renal cell carcinoma include HIF-1α, and its transcriptional targets, including CAIX, and others, and the markers macrophage migration inhibition factor (MIF), CREB, and the expression of the VEGF receptors VEGF-R1 and –R2 (107-110).

Markers of susceptibility to apoptosis will be measured by immunohistochemistry of the tumor specimen as described above, and will include HIF-1α, CAIX, macrophage migration inhibition factor (MIF), CREB, and the expression of the VEGF receptors VEGF-R1 and –R2 (107-110).

10.1 Pathology Submission
Paraffin embedded tumor samples obtained from the original diagnostic biopsy will be used in the analyses. No additional samples are requested. Sites should submit a single paraffin block representative of the tumor for IHC analysis. Once they are received at the University of Pennsylvania, the original paraffin block can be cut and from them both IHC slides and tissue microarray can be made. All slides should be mailed to Michael Feldman at the address below. All slides will be returned to the sites after analyses.

Michael D. Feldman, M.D., Ph.D
Department of Pathology and Laboratory Medicine
Hospital of the University of Pennsylvania, 6 Gates
3400 Spruce Street
Philadelphia, PA 19104

11.0 ONLINE REGISTRATION SYSTEM
11.1 Using the Online Registration System
Once the investigator-designated research staff (oncologist, radiologist, and the ACRIN site RA) has completed the eligibility checklist (Appendix II) and the participant has been found to be eligible to participate in the trial, the participant will be consented. Once a signed informed consent form has been obtained, the information of the study participant will be registered by logging onto the ACRIN web site (www.acrin.org), which is available 24 hours a day, 7 days a week.
questions, a participant is deemed ineligible based on a response, a message box appears to instruct the research staff to contact the ACRIN Data Management Center (DMC).

11.2.2 In the unlikely event that the ACRIN web registration site is not accessible, participating sites may still register a participant by faxing the completed eligibility checklist to the DMC at ACRIN (215-717-0936, ATTN: PARTICIPANT REGISTRATION). ACRIN DM staff will fax a response to the registering site with the confirmation of registration and participant case number as soon as possible.

12.0 DATA COLLECTION AND MANAGEMENT

12.1 General

12.1.1 The ACRIN web address is www.acrin.org.

12.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at the American College of Radiology Imaging Network’s Data Management Department in Philadelphia, PA.

12.1.3 Participant enrollment and data collection occur through a series of programmed screens accessed through the ACRIN web site to register participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week.

12.1.4 Each successful case registration is confirmed through receipt of an e-mail containing a registration confirmation and a case-specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, contact DMC before attempting re-registration.

12.2 Clinical Data Submission

12.2.1 Upon successful participant registration, a confirmation e-mail containing the registration and case-specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant-specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars will be updated as the study proceeds. to reflect data that have been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN web site. The research staff may use the calendar as a case management tool for data submission and follow-up scheduling.

12.2.2 The investigative site is required to submit data according to protocol as detailed on each participant’s calendar, as long as the case status is designated as open; or until the case status is designated closed or the study is completed. The case is considered
12.2.4 Once data entry of a form is complete and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the “Complete Form Submission” button on the form summary screen and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data completed and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

12.2.5 If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACRIN can serve as an ISP.

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

12.4 Electronic Data Management
12.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complimentary validation programs are initiated at the Brown BC and the DMC. The logic checks performed on the data at this point are more closed when all data have been received and reviewed and no outstanding data query exists for the case.
comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC Data Manager. The validation program generated by BC produces a log of errors, which is sent to the DMC Data Manager for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC Data Manager needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC for resolution. All Biostatistical and Data Management Center (BDMC) communication with the participating sites is normally done through the DMC.

12.4.2 If checks at DMC or BC detect missing or problematic data, the DMC Data Manager sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC Data Manager updates the participant’s data submission calendar with the due date for the site RA or investigator’s response.

12.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC’s case file with that of the RA and/or investigator. Future forms due reports may be sent on an as needed basis in addition to past due reports. The site investigator or research associate may use the Forms Due and Future Due Reports as a case management tool.

12.6 Data Quality Assurance

12.6.1 The Biostatistical Center (BC) at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the DMC at ACRIN. The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

12.6.2 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. If patterns are discovered in the data that appear to arise from causes specific to an institution, the BDMC will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance (PDRC) department, until the problem has been resolved. If
the BDMC, along with the Audit Group, cannot find a resolution to the problem, it will be brought to the ACRIN Steering Committee for further discussion and resolution.

13.0 IMAGE SUBMISSION

13.1 DCE-MRI Images and Back-Projection Raw Data
Sites will transfer all images as well as the raw data for the back-projection images to ACRIN via FTP. All data will be anonymized prior to submission. ACRIN will then forward the raw data to University of Pennsylvania for reconstruction and analysis. The reconstructed images will then be transferred to ACRIN by the University of Pennsylvania for quality assessment and archival. All DCE-MRI images for this protocol are requested to be provided in digital format. ACRIN has developed software that provides for the electronic transmission of images that have been scrubbed of all participant identifiers, to the Imaging Management Center (IMC) Image Archive. This software will be made available for installation to an already existing PC at your site, or an individual PC computer with this software installed will be supplied on a site-by-site basis. ACRIN will be contacting each site individually to determine their readiness and ability to work with this system. Once readiness has been determined, imaging personnel from ACRIN will coordinate the installation and training of this software.

An Image Transmittal Worksheet (ITW) is used during clinical trial image submission to verify a complete transfer of images sent to the ACRIN IMC. This worksheet is available via the ACRIN web site at www.acrin.org/4002_protocol.aspx. A separate ITW is to be faxed to the ACRIN IMC for each examination at the time the images are being transmitted. For images shipped on media, include the ITW with your shipment.

In the event DCE-MRI images or raw data are unable to be sent to the IMC electronically, they should be copied with anonymized data to a CD or DVD and sent to ACRIN. The information label on the CD should include: the study number, site number, case number, and the date of the exam.

ACRIN Image Archive
ACRIN PA 4002 Images
1818 Market Street, Suite 1600
Philadelphia, PA 19103-3604
Attn: ACRIN PA 4002 Imaging Specialist

13.2 If required and part of the protocol, images maintained at ACRIN Headquarters Image Archive may be distributed to other participating sites, using FTP, MOD, or CD-ROM where appropriate, for purposes of secondary review.

13.2.1 The header recorded on DICOM formatted image data often contains information identifying the participant by name. These participant identifiers must be scrubbed before the images are transferred.

This involves replacing the following:

- Participant Name tag with the ACRIN Institution ID or number
- Participant ID tag with the ACRIN case number, and
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- Other Participant ID tag with ACRIN Study Number.

This process can be completed by utilizing the software program available at the institution or the software program provided by ACRIN.

13.2.2 In the event that the site does not have DICOM capability or is unable to transfer images with scrubbed headers, the images may be sent on a CD or other electronic medium to ACRIN IMC for digitization/transfer to the Image Archive. Please contact the ACRIN IMC prior to sending the media to confirm compatibility.

13.3 Quality Control Review

Review of a sampling of the DCE-MRI cases will be performed in order to assure adequate quality of images obtained at each institution. The first set of phantom images will be reviewed by the central image review team. The normal volunteer images will also be reviewed prior to participant enrollment. Both the phantom images and the normal volunteer images must be approved by the central image review team prior to participant enrollment.

The first three (3) exams performed will be reviewed by the protocol Quality Control reviewer designated by the Study Principal Investigator at the ACRIN Image Core Laboratory in Philadelphia, PA. Alternately, these images can be sent to the protocol Quality Control reviewer via the Internet or on media for quality review. After which, a radiologist will review a random sample of all subsequent DCE-MRI exams for quality assurance purposes. The Imaging Specialist at ACRIN will perform an ongoing review of all images. This is to ensure the study images meet the study specific parameters.

13.4 MR Image Analysis Assessment

Central analysis for the back-projection images is being done at University of Pennsylvania. The imaging core lab will review for IQ, parameter compliance, and anatomic coverage. MR images will be reviewed centrally. The T1, T2, post-gadolinium, T1 maps, and DCE-MRI series will be assessed separately for image quality. Adequacy of anatomic coverage for the DCE-MRI study will also be performed.

13.5 Follow-Up Image Submission

Follow-up CT and MRI scans must be submitted to ACRIN.

14.0 ADVERSE EVENTS REPORTING

14.1 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 intervention. 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).

14.2 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.

14.3 Adverse Event Grading
Grade is used to denote the severity of the adverse event.

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

14.4 Adverse Event Attribution
Attribution is used to determine whether an adverse event is related to a study treatment or procedure. Attribution categories are:

Definite – AE is clearly related to the study treatment or procedure.
Probable – AE is likely related to the study treatment or procedure.
Possible – AE may be related to the study treatment or procedure.
Unlikely – AE is doubtfully related to the study treatment or procedure.
Unrelated – AE is clearly NOT related to the study treatment or procedure.

14.5 Expected Adverse Events
14.5.1 DCE-MRI Scan
➢ Anxiety/Stress;
➢ Claustrophobia;
➢ Discomfort.

14.5.2 Expected Adverse Events from Contrast Agent (gadolinium)
➢ Nausea;
➢ Headache;
➢ Hives;
➢ Temporary low blood pressure;
➢ Allergic reaction;
➢ Nephrogenic Systemic Fibrosis (NSF)/Nephrogenic Fibrosing Dermopathy (NFD).

NOTE: Precautions should be exercised for patients with a history of grand mal seizures, 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 Gd 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 after they have had a MRI scan with gadolinium-based contrast agent.
14.5.3 Expected Adverse Events From Needle Placement

- Minor discomfort;
- Bleeding;
- Infection;
- Bruising.

NOTE: Only adverse events that are considered possibly, probably, or definitely related to DCE-MRI procedures require reporting to ACRIN. Please refer to your local IRB’s policies regarding adverse events.

14.6 Recording and Reporting of Adverse Events

Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and/or nurse engaged in clinical research. Please refer to section 14.7.1 for specific details for reporting. Anyone uncertain about whether a particular adverse event should be reported should contact the ACRIN headquarters at 215-574-3150 for assistance. However, an adverse event report should be submitted if there is a reasonable suspicion that the AE may be related to the study procedures.

Routine reporting is defined as documentation of adverse events on source documents and AE CRF, and submission to ACRIN for preparation of a report for Data and Safety Monitoring Committee (DSMC) review, and the final study report.

Expedited reporting is defined as immediate notification of ACRIN within the specified timeframe outlined in the protocol. Routine reporting requirements also apply.

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on adverse events through discussion and, as appropriate, by examination. Information on all significant and non-significant, expected and unexpected adverse events considered possibly, probably, and definitely related to the ACRIN PA 4002 trial with the severity level of grades 3, 4, 5 should be recorded immediately into the source document, e.g. adverse event log and/or progress notes of the study participant’s chart, and retained at the site. These adverse events will also be recorded in the AE CRF and reviewed by the principal site investigator in real time to determine grade and attribution of the event. If the AE meets the criteria for serious and require expedited reporting, ACRIN SAE Report will be completed. (Refer to 14.7.1 for detailed instructions.)

AEs already documented in the CRF (i.e., at a previous assessment) and designated as ‘ongoing’, should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the CRF should be completed including an end date for the event and not the date of the visit. If an adverse experience increases in frequency or severity during a study period, an up to date record of the experience will be documented. Each adverse event should be followed until resolution, stabilization, or until it has been determined that the study procedures or study participation is not the cause. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study procedures or study participation should be recorded and reported immediately.

14.7 When to Report

It is the responsibility of the investigator to document all Adverse Events (AEs) as identified in section 14.5, which occur during the course of the study including any
unexpected AEs with grades 3, 4, and 5 and with attribution of possible, probable, and definite. At each designated visit, the investigator will evaluate for any adverse events. AEs not previously documented in the study will be recorded within the study participant’s chart to identify any potentially related to any study procedures. The nature of each event, date and time (when appropriate) of onset, outcome, frequency, maximum intensity, action taken, and attribution will be recorded.

14.7.1 You must use the following adverse event reporting for any protocol specific AEs/SAEs:

1. Grade 3 unexpected adverse events with hospitalization that are possible, probable, or definite require a complete SAE report to be submitted within 10 calendar days of first knowledge of the event. Routine reporting procedures also apply.

2. Grade 3 expected adverse events with hospitalization that are possible, probable, or definite will be reported by routine reporting procedures only.

3. Grade 3 unexpected and expected adverse events without hospitalization that are possible, probable, or definite will be reported by routine reporting procedures only.

4. Grade 4 unexpected and expected adverse events that are possible, probable, or definite require a complete SAE report to be submitted within 10 calendar days of first knowledge of the event. Routine reporting procedures also apply.

5. Grade 5 unexpected and expected adverse events that are possible, probable, or definite will be reported via phone report within a 24-hour time period to ACRIN by the investigator or investigator-designee. In addition, a complete SAE report is due within 10 calendar days of the initial 24-hour telephone report. Routine reporting procedures also apply.

6. Expedited adverse event reporting must be completed within 10 working days of first knowledge of the event.

14.7.2 Assignment of grades and attribution for each AE/SAE must be completed by the site principal investigator. All AEs/SAEs should be documented in the study participant’s chart and CRFs. For expedited SAE reports, a copy of the report must be kept at the site. Significant new information on any on-going SAE should be promptly reported to ACRIN.

14.8 How to Report
14.8.1 An expedited adverse event report requires submission to ACRIN using the ACRIN SAE Report.

14.8.2 Completed expedited reports should be sent to:

ACRIN AE Coordinator
Re: Serious Adverse Event Report
ACRIN PA 4002
14.8.3 A copy of all SAE reports should be sent to ACRIN by fax at (215) 940-8819. All deaths should be reported by telephone within 24-hours of first knowledge of the event. To make a telephone report to ACRIN, call (215) 717-2763, available 24 hours a day (recorder available Monday through Friday from 4:30 PM to 8:00 AM Eastern Time and on weekends).

14.8.4 All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Please refer to your local IRB’s policies regarding adverse events.

15.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice [International Conference of Harmonisation (ICH) guidelines], applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments, including the informed consent form will be submitted to a properly constituted independent Institutional Review Board (IRB) for a formal approval of the study conduct. The decision of the 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 assurance number, along with the IRB approval letters. Prior to study participant’s registration, a copy of the IRB approval letter for the protocol and the informed consent form must on file at ACRIN, along with a copy of the IRB approved informed consent form. Investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual re-approval(s).

All study participants in this study will be provided with an IRB approved informed consent form describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix I for a copy of the sample informed consent form). This consent form will be submitted along with the protocol for review and approval by the local IRB. The study participant MUST be consented with the IRB approved informed consent form before the participant is subjected to any study procedures. The approved informed consent form MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent.

16.0 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 policies and applicable federal, state, and local laws and regulations.

17.0 PUBLICATION POLICY

Neither complete nor partial study results will be published or passed on to any third party without the formal consent of the ACRIN Publication Committee. Any investigator involved in
this study is obligated to provide ACRIN with complete test results and all clinical data obtained from the participating in this protocol. Investigators will follow ACRIN Publication Policy (available on the web at www.acrin.org/PublicationsPolicy.aspx).

18.0 INSTITUTIONAL MONITORING AND AUDITS
The investigator will permit study-related monitoring, auditing, and inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN. Monitoring of the protocol is implemented after the activation of the trial and participants have been enrolled into the study at each site. Each site will be informed when the monitoring of the protocol is implemented. Sites will be provided with detailed instructions and checklists to assist in preparation of the monitoring review.

For audits, the investigator will ensure the capability for inspection of all participating site’s study-related facilities (e.g. imaging center, 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. Initial on-site audits will be completed within 9 months of each site’s enrollment of its first ACRIN participant. Subsequent audits will be scheduled per the outcome of the initial audit.

The audits will be conducted per procedures established in the ACRIN Audit Manual. The ACRIN Audit Manual is available online at www.acrin.org. 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 consent forms will also be reviewed at the time of the audit visit.

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

18.1 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 case report forms (CRFs). If an item is not mentioned (e.g., history and physical with 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 reported to ACRIN. If data is 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
However, every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol at the time of the audit visit. This will prevent any discrepancies and the inability to verify the document and the data reported.

18.2 Case Report Forms
Case report forms (CRFs) are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank 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 must be printed legibly in black ink on the paper case report forms. 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.

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 case report forms (CRFs) will be audited against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires may be documented on the CRF. The image interpretation data required by the study that is a more detailed extraction of information from the image and is not typically documented in the standard radiology report may be recorded on the CRF and is accepted as 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 on which the exam took place from the medical record. Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (participant questionnaire, CT, MR, etc.).

Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a deficiency.

19.0 STATISTICAL CONSIDERATIONS

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REFERENCES


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APPENDIX I

SAMPLE CONSENT FOR RESEARCH STUDY

[Note: ACRIN (American College of Radiology Imaging Network) does not monitor compliance with the Health Insurance Portability and Accountability Act (HIPAA); it is the responsibility of local IRBs and the Institution. Information on ACRIN’s HIPAA policy, as well as a template for HIPAA authorization, can be found at www.acrin.org.]

STUDY TITLE:

ACRIN PA 4002: ANGLE INTERLEAVED PROJECTION RECONSTRUCTION WITH K-SPACE WEIGHTED IMAGE RECONSTRUCTION FOR DYNAMIC CONTRAST MRI OF CANCER THERAPY RESPONSE

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part in the study. Please take your time to make your decision. 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 for more explanation.

You are being asked to participate in the trial because you have cancer that has spread to your liver. In this study, if you agree to participate, you will have either two (2) or three (3) specialized MRI scans. The number of scans you will have depends on type of cancer that spread to your liver.

You will be asked to participate in one group if you have colorectal cancer that has spread to the liver and will be treated with chemotherapy that includes the medication called bevacizumab (a medication that has been shown to stop the blood supply of cancer tumors). You will be asked to have three specialized MRI scans, two scans before your chemotherapy treatment and one scan after your first chemotherapy treatment, to determine whether an MRI can detect blood flow changes in the tumor.

But if you have any kind of cancer that has spread to the liver, you will be asked to join the other group. You will have two specialized MRI scans within a couple of weeks of each other to see if the specialized MRI can reliably measure blood flow in your tumor.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine if the imaging procedure called “dynamic contrast-enhanced magnetic resonance imaging” (DCE-MRI) is able to detect changes in tumors in the liver.

An MRI is produced using a powerful magnet and radio waves linked to a computer to create remarkably clear and detailed cross sectional images of the body. To visualize an MRI, think of your body as a loaf of bread with its many slices. The MRI allows the doctors to see many
different “slices” of a body part by taking pictures from outside the body. The “slices” can be displayed on a video monitor and saved on film for analysis.

For some MRI studies, a contrast agent, usually gadolinium, may be used to enhance the visibility of certain tissues. The contrast agent is given via a small intravenous (IV) line placed in a vein in your arm.

This research is being done to see if DCE-MRI can reliably identify changes in tumors and blood flow changes. DCE-MRI has been used in clinical care and in research, but is not commonly used in treating tumors in livers of patients. In the past, other imaging exams have been used to evaluate tumors in the liver. Because DCE-MRI provides images of tumors, it may be able to identify growing lesions that would otherwise go undetected. Identifying tumors early may provide information that will help the study doctors better understand the processes that cause colorectal cancer and other cancers that spread to the liver and may lead to better treatments for these types of cancer in the future.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 60 participants will be enrolled into the study over one year at five (5) institutions located in Pennsylvania.

HOW LONG WILL I BE IN THE STUDY?

If you have the colorectal cancer with liver metastases, you will be in the study for approximately two years. Your health information will be collected for up to one year after you have had your chemotherapy treatment.

But if you have any other type of cancer with liver metastases, you will be in the study for approximately four weeks, but possibly longer depending on the scheduling of your DCE-MRI scans. Your health information will only be collected before and after the DCE-MRI scans. Once you have completed your 2nd scan, your participation will be complete.

This study is expected to end after all study participants have completed the study visits and all the information has been collected. This study may be stopped at any time by your study doctor or by ACRIN without your consent for the following reasons:

- For your health or safety
- For not following study instructions
- For study administrative decision by ACRIN or the study doctor

These actions do not require your consent, but you will be informed of any of these decisions.

You can stop participating at any time. Your decision to stop participating in the study will not interfere with your future medical care. However, if you decide to stop participating in the study, we encourage you to talk to both your study doctor and treating doctor first.
WHAT AM I BEING ASKED TO DO IN THE STUDY?

As a study participant in this research study, you will be asked to have either two (2) or three (3) DCE-MRI scans of your abdomen (liver). If you have colorectal cancer with liver metastases, you will be asked to have two (2) DCE-MRI scans before you receive your first chemotherapy treatment. These scans must be done within 2 weeks before your chemotherapy begins but must be at least 48 hours apart. You will then have the 3rd DCE-MRI after you finish your first chemotherapy treatment but before you have your second chemotherapy treatment.

If you have any other type of cancer with liver metastases, you will only be asked to have two (2) DCE-MRI scans of your abdomen (liver). After you have had your first visit with the research staff and have provided a signed informed consent form, the research staff will help in scheduling your DCE-MRI scans. The two (2) MRI scans must be completed within two (2) weeks of each scan but at least 48 hours apart.

Before an MRI, eat normally and take your usual medications unless otherwise instructed. You will be given a hospital gown to wear or instructed to wear loose clothing without metal fasteners. Remove all accessories, such as jewelry or hair pins/ clips. Also remove wigs, dentures, glasses, and hearing aids. Metal objects may interfere with the magnetic field during the exam, affecting the quality of the MRI images. The magnetic field may damage electronic items. Tell the technologist (the person performing the MRI) if you have:

- any prosthetic joints
- a pacemaker, defibrillator, or artificial heart valve
- an implanted venous access device
- an intrauterine device (IUD)
- any metal plates, pins, screws, staples or bullets/shrapnel
- tattoos or permanent make-up
- a transdermal patch
- anxiety in confined spaces (claustrophobia)
- any concerns about being pregnant

If you are of childbearing age, you may have to have a pregnancy test prior to the MRI scans. If you are pregnant or suspect you may be pregnant, tell the technologist.

A conventional MRI unit is a large cylindrical magnet with a central opening. A sliding table rests in the opening. You will lie on the narrow table and be comfortably positioned. A small coil may be placed around the area being examined. The table will then be slid into the opening. The technologist will be in an adjoining room, but can see, hear, and speak to you at all times. In some cases, a friend or family member may stay in the room with you.

The MRI opening is usually between 21-26 inches wide. The opening in the MRI scanner is 5-8 feet long. During the exam, you may feel “closed in” or claustrophobic. If this is a concern, speak to your doctor when the MRI is scheduled. Your doctor may suggest a mild sedative to help you feel more comfortable during the MRI exam. The MRI technologist is experienced in working with people who are uncomfortable in close spaces. “Short bore” systems are shorter.
and wider and do not totally enclose the patient. “Open” MRI systems are available for those who are unable to use a conventional MRI, however the image quality varies.

DCE-MRI utilizes rapid MR imaging during injection of a contrast agent called gadolinium. The contrast agent is given via a small intravenous (IV) line placed in a vein in your arm. An MRI exam usually consists of several sequences, each lasting 2-15 minutes. Slight movement between sequences is allowed.

Each DCE-MRI scan lasts approximately 40-50 minutes, during which you will be asked to lie flat in the MR scanner. You will hear a loud tapping or thumping noise during the exam. Earplugs or earphones may be provided to you to help block the noise. The technologist will talk to you throughout the exam. During the exam you will need to remain very still. The exam is painless. You may feel warmth in the area being examined. You will at times be asked to hold your breath for up to 20-25 seconds during this study.

If you have colorectal cancer with liver metastases, you will receive your chemotherapy treatment that consists of 5-fluorouracil, leucovorin, and oxaliplatin (also known as FOLFOX) and a targeted agent called bevacizumab, as recommended by your treating doctor. You may receive this treatment even if you do not participate in this study by your treating doctor. As recommended for your treatment, you will receive this treatment every two (2) weeks for a maximum of six (6) months, or until your treating doctor determines that the treatment is not working or it is making you too sick. You will be given FOLFOX plus bevacizumab chemotherapy regimen in a vein in your arm. This regimen will take between 4-5 hours for the first cycle. Other cycles may be a little shorter if you do not experience any side effects with your treatment.

**STUDY PROCEDURES**

**Visit 1: REGISTRATION VISIT**

If you decide to volunteer in this study, you will be asked to provide the following information: your name, birth date, phone number, current address, weight, and height. You will also be asked to answer questions about your medical health to see if you can participate in this research study. You may have to have a pregnancy test or blood work to ensure that you are not pregnant and that your kidney function is healthy. If at any time during the study you might be pregnant, please inform your treating and study doctors.

During this visit, you will be asked questions regarding any implanted metal or medical devices, or if you have claustrophobia that may make it unsafe for you to have a DCE-MRI scans. Your study doctor will review your medical records to see that your cancer qualifies for the imaging research study. Your study/treating doctor(s) may also perform additional tests or imaging scans at this time as part of your routine clinical care. At this time, you will be scheduled for two (2) DCE-MRI scans. Before each of the DCE-MRI scans, you may have to have a pregnancy test if you are of childbearing age.

**Visits 2 and 3: DCE-MRI VISITS**

The two (2) DCE-MRI scans are completed to see how accurately we can measure tumor blood flow to your tumor by using DCE-MRI scans.
If you have colorectal cancer with liver metastases, these scans will occur before you begin chemotherapy for your cancer. The 2 scans will be separated by at least 2 days but should both be completed no more than 14 days after Visit 2. Then, you will continue with the study and receive your chemotherapy treatment that consists of 5-fluorouracil, leucovorin, and oxaliplatin (also known as FOLFOX) and a targeted agent called bevacizumab.

If you have a different type of cancer with liver metastases, then the 2 scans will be completed within 2 weeks of your registration into the trial as long as you are stable. This means the 2 scans can be done before your treatment begins, during treatment as long (as you are not experiencing too many side effects), or after your last treatment. These 2 scans also will be separated by at least 2 days but should both be completed no more than 14 days apart from each other. After you have had the two (2) MRI exams, you have completed your participation in this study.

**FOR PARTICIPANTS WITH COLORECTAL CANCER WITH LIVER METASTASES ONLY**

**FIRST CHEMOTHERAPY TREATMENT**

You will receive your first chemotherapy treatment after you have the 2 DCE-MRI scans. Your study/treating doctor(s) will check on your condition during this time.

**Visit 4: POST-TREATMENT DCE-MRI VISIT**

You will have your 3rd DCE-MRI scan after your first cycle of chemotherapy has been completed. Again, you may have to have a pregnancy test before the DCE-MRI scan if you are of childbearing age. It should be about 8 to 14 days after your first treatment, but before you receive your second chemotherapy treatment. After the third DCE-MRI scan, you will continue with your chemotherapy under the care of your treating doctor.

**FOLLOW-UP**

You will continue to receive your chemotherapy treatment for your cancer under the care of your treating doctor, usually including imaging studies (MRI or CT scans), at regular intervals. Your treating doctor will determine if the treatment is working and if the treatment is causing any side effects that might affect your health.

During this time, a research coordinator will speak with your treating doctor and review any records of your cancer treatment obtained from your treating doctor. At this time, your medical records will be reviewed to see how the chemotherapy treatment had on your cancer and your health, and to see if there are any changes to the tumor(s) or blood flow in the tumor(s) in your body.

**Study Chart**

| Visit 1: Registration Visit | • Review and sign the informed consent form (ICF) if you agree to participate in this study;  
|                           | • Answer a questionnaire about your health and symptoms;  
|                           | • Confirm that you are not pregnant and that your kidney function is healthy. |
Visit 2: Within 2 weeks After Visit 1

- Confirm that you are not pregnant;
- Have DCE-MRI scan with contrast agent.

Visit 3: 48 hours to 14 days of first DCE-MRI scan

- Confirm that you are not pregnant;
- Have DCE-MRI scan with contrast agent.

If you have any other types of cancer with liver metastases and have had the two (2) MRI scans at Visits 2 & 3, you have completed your participation in this study.

If you have colorectal cancer with liver metastases, have your first chemotherapy treatment and continue with the study visits.

Visit 4: 8 to 14 days after 1st chemotherapy treatment

- Confirm that you are not pregnant;
- Have DCE-MRI scan with contrast agent.

Have your second chemotherapy treatment and continue with your follow-up treatments as your treating doctor has recommended

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?

While on the study, you may experience some side effects. If you do have any side effect from the DCE-MRI scans and the contrast agent, you should tell your study doctor. There may be other side effects that we cannot predict. There are no specific risks associated with DCE-MRI scan. However, you may experience some anxiety and/or discomfort. Drugs may be given to make these side effects less serious and less uncomfortable. Many side effects go away shortly after the imaging scan is completed, but in some cases, side effects can be serious, long lasting, or permanent.

Reproductive risks: If you are pregnant or nursing or plan to become pregnant, you cannot take part in this research study. It is important that a baby and a fetus developing in the uterus not be exposed to any unnecessary risks. Therefore, in order to participate in this study you understand that you must not be pregnant or nursing at the time of your scan. If you are a female participant, you will be asked if you could be pregnant prior to having each DCE-MRI scan. If you are unsure, the research team may ask you to take a pregnancy test.

DCE-MRI:
- Anxiety/Stress;
- Claustrophobia;
- Discomfort.
CONFIDENTIAL

**Gadolinium**
Approximately two percent 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.

*Less likely*
- Headaches;
- Nausea.

*Less likely, but Serious*
- Allergic reaction.

*Very rare*
- 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, we will determine if your kidneys are working properly in order to make sure the gadolinium contrast agent is safe for you.

**Intravenous (IV) Catheter Placement**

*Likely*
- Minor discomfort.

*Less likely*
- Bleeding;
- Infection;
- Bruising.

**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 results of this study may benefit future patients with colorectal and other types of cancer that have spread to the liver. This knowledge may help doctors decide on the best chemotherapy regimen, especially among those drugs that slow the growth of cancer tumors.

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

You may choose not to participate in this study. Whether or not you choose to participate in this study, you may receive some or all of the chemotherapy medications described in this study. Please talk to your treating doctor about this and other possible options of different available methods for treating your cancer.
WHAT ABOUT CONFIDENTIALITY?

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

Authorized representatives of ACRIN, Center for Statistical Sciences at Brown University, the Institutional Review Board (IRB) of <<Institution>>, and other groups or organizations that have a role in this study will have access to and may inspect and/or copy both your medical and research records due to your participation in this study. This access is necessary to ensure the accuracy of the findings 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 such that you cannot be identified.

Your research records and DCE-MRI images will be kept permanently on file at ACRIN and may be used for future research. All personal identifiers are removed and replaced with unique identifying number. The research that may be done with the information will not specifically help you. But, it might help people who have cancer and other diseases in the future.

WILL I HAVE TO PAY FOR ANYTHING?

Taking part in this study may lead to added costs to you or your insurance company. However, there will be no cost to you for the DCE-MRI scans used in this study. Please ask your study doctor(s) about any expected added costs or insurance problems.

You and/or your health insurance may be billed for the costs of medical care during the study if these expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay. You and/or your insurance company will be charged for your continuing medical care and/or hospitalization for your treatment of your cancer.

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. You can tell the study doctor in person or call him/her at <<insert telephone number>>.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.
WILL I BE PAID FOR BEING IN THIS STUDY?

You will receive $<<Institution to provide appropriate amount per institution’s policy>> upon completion of the study as compensation for your time and travel associated with your participation in this research study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may 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 benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Your study/treating doctor(s) may stop your participation in this study at any time, if it is in the best interest of your health.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed by each individual site)

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 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>>.

ADDITIONAL SCIENTIFIC STUDIES (OPTIONAL) —FOR PARTICIPANTS WITH COLORECTAL CANCER WITH LIVER METASTASES

A tissue block is a sample of tissue from your tumor that has been prepared by standard laboratory for clinical analysis. The tissue block from your tumor will be used to prepare thin small sample to place on glass slides for a pathologist to review. The tissue block will be used to make a tissue microarray (TMA).

If you agree to participate in this portion of the study, a small sample of tumor from your original tissue block will be removed (3 mm x 0.6 mm core of tissue) and transferred into a tissue microarray. The remainder of your tissue block will be returned to your institution.

We would like to have samples of your tumor tissue for additional laboratory research studies. The tissue samples will be from an earlier biopsy or surgery. Another procedure will not be done to collect this tissue. Tumor samples will be taken from the original diagnostic biopsy.
WILL ANY OF THE TISSUE SAMPLES TAKEN FROM ME BE USED FOR OTHER RESEARCH STUDIES?

We would like to collect and analyze your tissue samples. The study doctors will analyze the tissue to search for additional characteristics that may help them better understand your type of cancer. The tissue samples will be given only to study doctors approved by the American College of Radiology Imaging Network (ACRIN). Any research done on the tissue must be approved by an Institutional Review Board (IRB). Reports about the research done with your tissue will not be given to you or to your treating doctor. These reports will not be put into your health record. Additional research done with your tissue samples will not have an effect on your care.

ARE THERE BENEFITS TO HAVING MY TISSUE USED FOR RESEARCH?

If you agree to have your tissue used for research, the study doctors may learn more about cancer, what causes cancer and other diseases, how to prevent them, how to treat them, and how to cure them. This knowledge will help doctors to decide on the best treatments for patients with cancer, especially those patients with colorectal cancer that spreads to the liver.

WHAT ARE THE POSSIBLE RISKS FOR HAVING MY TISSUE USED FOR RESEARCH?

There are very few risks in having your tissue used for research. The greatest risk is the release of information from your health records. People who do research may need to know more about your cancer and your health. The tissue will be coded to protect your identity. This code can be linked to your medical information collected by ACRIN. Your records will be protected so that your name will be kept private. The chance that this information will be given to someone else is very small.

Participating in studies can involve risks for participants and their families. Every effort is made to minimize these risks. Risks include breaches of confidentiality of test results, and the effects of the knowledge that one has a disease-related gene that might alter one’s life course, reproductive decisions, employability, or insurability.

THINGS TO THINK ABOUT

The choice to let us keep the leftover tissue for future research is up to you. No matter what you decide to do, it will not affect your medical care, and you may still take part in the research study.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact your study doctor and let him or her know that you do not want us to use your tissue. Then, the tissue will no longer be used for research.
CONFIDENTIAL

If you agree to have your tissue used for future research studies, study doctors may need to know more about your cancer and your health. ACRIN will only give them reports about your cancer and your health. Your identity will be kept private. Your name will not be given to them.

Your tissue will be used only for research, and it will not be sold. You will not be paid for allowing your leftover tissue to be used in research, even though the research done with your tissue may help to develop new products in the future. Similarly, there will be no cost to you for any tissue collected.

MAKING YOUR CHOICE

Please read each sentence below and think about your choice. After reading each sentence, check “Yes” or “No”. Whatever you decide to do with your leftover tissue, your decision will not affect your medical care. You can participate in the DCE-MRI part of the study without participating in the tissue research study.

If you have any questions, please talk to your study doctor, treating doctor, your nurse, or our Institutional Review Board (IRB) at <<Insert IRB contact person’s telephone number>>.

<table>
<thead>
<tr>
<th>I agree to allow my tissue to be used for current and future research to learn about, prevent, or treat cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>My tissue may be kept for use in future research about other health problems (for example, causes of diabetes, Alzheimer’s disease, and heart disease).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

WHERE CAN I GET MORE INFORMATION?


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 have also had the opportunity to take this consent form home for review or discussion if you want to.

You willingly give your consent to participate in this study. A copy of this signed consent form will be given to you.
<Insert other signature and date lines as appropriate per local IRB policies and procedures>
APPENDIX II

REGISTRATION/ELIGIBILITY CHECK

The ACRIN PA 4002 Eligibility Checklist is available on the ACRIN web site on the ACRIN PA 4002 protocol-specific web page (www.acrin.org/4002_protocol.aspx). For more detailed information, contact the ACRIN PA 4002 Data Manager at ACRIN. The contact information can also be found on the above-mentioned web page via the left-hand navigation link entitled: 4002 Contact Personnel.
## APPENDIX III

### DETAILED PARAMETER CHART

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<th>3</th>
<th>4</th>
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<td>T1 mapping</td>
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<td>SPGR</td>
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<td>5-10</td>
<td>5-10</td>
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<td>variable</td>
<td>1 – 2 minutes per flip angle</td>
<td>6–8 min</td>
<td>20-30</td>
</tr>
</tbody>
</table>

* Coronal for phantom imaging.

** Number of projections for sequences 4 and 5.

*** 32 projections per subaperture.
Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response when all lesions have disappeared.

Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of “Target” and “Non-Target” lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

* Complete Response (CR): Disappearance of all target lesions
* Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
* Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
* Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
**Evaluation of non-target lesions**

* Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

* Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits

* Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

**Evaluation of best overall response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

<table>
<thead>
<tr>
<th>Target lesions</th>
<th>Non-Target lesions</th>
<th>New Lesions</th>
<th>Overall response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Incomplete response/SD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.
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Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study’s completion. Simultaneous review of the participants’ files and radiological images is the best approach.

Reporting of results

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
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- All conclusions should be based on all eligible patients.

- Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported.

- The 95% confidence intervals should be provided.
Minimum of four (4) Pennsylvanian Institutions will be participating in the ACRIN PA Trial.

Five institutions are expected to participate in this study. As the study is funded through grant support directed explicitly for use within the state of Pennsylvania, all 5 centers are located in the state of Pennsylvania. These centers are:

- University of Pennsylvania Medical Center, Philadelphia, PA
- Thomas Jefferson Medical Center, Philadelphia, PA
- Fox Chase Cancer Center, Philadelphia, PA
- Hershey Medical Center, Hershey, PA
- University of Pittsburgh Medical Center, Pittsburgh, PA

1. Participants will be identified in the oncology clinics of each of the four participating institutions.

2. Participant may be treated by any participating oncologist affiliated with the participating institutions.

3. Participants must be treated at the participating institution, or within a clinical entity affiliated with the participating institution. All DCE-MRI must be performed at the participating institutions.

4. Participants residing outside the state of Pennsylvania are eligible to participate as long as they are able to maintain the treatment schedule with the affiliated oncologist, and participate in all DCE-MRI studies at the participating institution.
Appendix VI-Phantom Figures

A) gadolinium phantom
   posterior coil

B) anterior coil
   “loading” phantoms

C) “loading” phantom
   gadolinium phantom
   posterior coil

D) anterior coil
Figure 2- Localizer Images
Appendix VII
FOLFOX REGIMENS

Commonly used, protocol-appropriate FOLFOX regimens include, but are not limited to:

FOLFOX 4 (repeat every 2 weeks)

Day 1
- Leucovorin 200 mg/m² over 2 hours
- Oxaliplatin 85 mg/m² over 2 hours
  After 2 hour-infusion time: 5-FU bolus 400 mg/m²
  Followed by: 5-FU infusion 600 mg/m² over 22 hours

Day 2
- Leucovorin 200 mg/m² over 2 hours
  After 2 hour-infusion time: 5-FU bolus 400 mg/m²
  Followed by 5-FU infusion 600 mg/m² over 22 hours

FOLFOX 6 (repeat every 2 weeks)

Day 1
- Leucovorin 400 mg/m² over 2 hours
- Oxaliplatin 100 mg/m² over 2 hours
  After 2 hour-infusion time: 5-FU bolus 400 mg/m²
  Then, begin: 5-FU 46-hour infusion 2400–3000 mg/m²

Day 2
- Continue: 5-FU 46-hour infusion 2400–3000 mg/m²

mFOLFOX 6 (modified FOLFOX 6) (repeat every 2 weeks)

Day 1
- Leucovorin 400 mg/m² over 2 hours
- Oxaliplatin 85 mg/m² over 2 hours
  After 2 hour-infusion time: 5-FU bolus 400 mg/m²
  Then, begin: 5-FU over 46-hour infusion for a total of 2400 mg/m²

Day 2
- Continue: 5-FU over 46-hour infusion for a total of 2400 mg/m²

FOLFOX 7 (repeat every 2 weeks)

Day 1
- Leucovorin 400 mg/m² over 2 hours
- Oxaliplatin 130 mg/m² over 2 hours
  After 2 hours, begin: 5-FU 46-h infusion 2400 mg/m²

Day 2
- Continue: 5-FU 46-hour infusion 2400 mg/m²

References: