AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6690

A Prospective, Multicenter Comparison of Multiphase Contrast-Enhanced CT and Multiphase Contrast-Enhanced MRI for Diagnosis of Hepatocellular Carcinoma and Liver Transplant Allocation

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SCHEMA

HCC diagnosis by baseline CT or MRI
(SOC imaging at participating center; SOC imaging can be used for trial baseline imaging if completed within 30 days prior to enrollment)

Listing for liver transplantation with HCC-exception points

Eligibility/Enrollment (within 30 days of listing)

Complement imaging within 30 days after enrollment
(if not completed as part of HCC diagnostic imaging; SOC imaging may need to be repeated if completed outside of 30-days pre-enrollment)

Local ablative therapy
(strongly consider biopsy if feasible)

Imaging
(SOC + complement imaging, no less than 28 days and no more than 60 days after completion of ablation)

Repeat serial imaging every 90 days per UNOS listing update requirements
(CT and MRI completed within 7 days of each other)

Transplant surgery

Explant pathology analysis

HCC = hepatocellular carcinoma; CT = computed tomography; MRI = magnetic resonance imaging; SOC = standard of care.

The term “SOC imaging” is used in this trial protocol to describe the imaging exam (MR or CT) that is the “first choice” at a participating institution to update a patient’s HCC-exception MELD points on the liver transplant waitlist every 90-days. The term “complementary imaging” is used in this trial protocol for the “other” modality (MR or CT), which will be considered the protocol-required research scan consistently at a center. “Additional imaging” (MR and CT) will need to be performed within 28 to 60 days after completion of ablative therapy to assess for residual or recurrent HCC; this imaging time point may coincide with the next serial imaging time point required for liver transplant waitlist updates, in which case only one pair of imaging exams (MR and CT) needs to be obtained.
STUDY OBJECTIVES/SPECIFIC AIDS

We hypothesize that modern imaging technology can accurately diagnose and stage hepatocellular carcinoma (HCC) in patients with chronic liver disease when performed on state-of-the-art multidetector computed tomography (CT) or magnetic resonance imaging (MRI) equipment, with contemporary multiphase contrast-enhanced imaging protocols. Focal liver lesions can be accurately assigned to pre-malignant and malignant diagnostic categories based on patterns of specific imaging findings. Furthermore, we expect that the false positive rate in the malignant lesion category can be reduced from current unacceptable levels by utilizing the new Organ Procurement and Transplantation Network (OPTN) liver imaging policy draft. This trial compares the accuracy of radiologic staging of HCC by CT and MRI with the reference standard provided by explant pathology workup/staging of participants who undergo liver transplantation for treatment of HCC. It tests the performance of an imaging-based diagnostic algorithm for HCC, which forms the basis of the aforementioned new draft policy.

ELIGIBILITY (see Section 5.0 for details)

Patients who are diagnosed with HCC and listed for liver transplant surgery with priority MELD (Model for End-Stage Liver Disease) points based on the cancer diagnosis; a given patient may be waiting for a liver from a deceased donor to become available or be scheduled to undergo a living donor adult liver transplant. Patients must enroll in the trial within 30 days after initial listing with HCC-exception points to the UNOS waitlist.

SAMPLE SIZE

A total of 440 patients will be accrued from transplant centers in the 11 OPTN transplant regions across the United States with approximately 25 to 30 centers participating in the study.
1.0 ABSTRACT
This protocol for human research study is conducted according to United States and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (e.g. Title 45, Part 46 Code of Federal Regulations), and the American College of Radiology Imaging Network (ACRIN) research policies and procedures.

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths with over 500,000 annual deaths worldwide. HCC accounts for approximately 80% of all primary liver cancers and has become the third leading cause of death worldwide according to data published in from the Centers for Disease Control and Prevention. With the major clinical risk factor being hepatitis B or hepatitis C virus infection, the prevalence of HCC has increased significantly in the last two decades. The diagnostic algorithm for HCC in clinical practice today has been developed mostly based on the literature and expert consensus rather than analytic data. The diagnosis is established by serology, cyto-histology, and radiologic characteristics to diagnose and stage the disease. As the precise staging of the disease determines prognosis as well as choice of curative, palliative, and/or symptomatic therapy, an accurate assessment of this disease is vital.

The most effective treatment for patients with HCC is liver transplantation, as it removes in toto the primary tumor(s), inclusive of any clinically unapparent microscopic disease in the remainder of the liver, and replaces the often-cirrhotic native liver with a graft organ, typically from a deceased donor. In the last two decades, this treatment has yielded survival rates of more than 70% at 5 years and recurrence of disease of less than 15% for patients with HCC undergoing transplant. Once listed for transplant, patients may experience excessive waiting times for organs from deceased donors, especially in regions with an unfavorable ratio of available organs to qualified recipients. Consequently, disease progression while on the waitlist and death drive drop-out rates from the transplant list.

The Organ Procurement and Transplantation Network (OPTN) is the unified transplant network established by the United States Congress under the National Organ Transplant Act (NOTA) of 1984. The United Network for Organ Sharing (UNOS) administers the OPTN under contract with the Health Resources and Services Administration of the U.S. Department of Health and Human Services. To achieve a more timely transplantation for patients in most need, UNOS uses the Model for End-stage Liver Disease (MELD) scoring system to prioritize the transplant waitlist organs to patients with end-stage liver disease (ESLD) based on survival probability. The traditional MELD score is based on serologic metabolic markers of liver function and correlates with a certain mortality risk; however, patients with life-threatening HCC often have a MELD score too low to earn them a timely transplant even though their mortality from the cancer equals that of patients with a much higher [metabolic] MELD score. In recognition of this fact, UNOS adopted a new policy in 2002 that allowed liver cancer patients to obtain so-called HCC-exception MELD points. Thus for the first time, priority could be assigned based on survival probability predicated on the diagnosis of HCC only, which was felt to minimize inequities between the two main liver transplant-candidate subsets.

The current OPTN/UNOS Policy for liver transplantation in the United States specifically allows a pre-transplant diagnosis of HCC based solely upon imaging criteria. A retrospective analysis of the UNOS database comparing the accuracy of radiologic staging with pathologic staging of explant organs found that the performance of imaging under the current policy was unacceptable. The imaging data did not portray an accurate staging of the disease, and in many cases resulted in the inappropriate allocation of transplant livers. The current policy contained no technical and image acquisition requirements for liver imaging and vague qualitative diagnostic imaging criteria, resulting in a high number of false-
positive diagnoses. Often, common benign focal abnormalities in the diseased liver were mislabeled as HCC and resulted in misallocation of donor organs. The current OPTN/UNOS policy requirements are insufficient for imaging-based diagnosis of HCC qualifying the patient for priority on the transplant waitlist. In 2008, UNOS convened an interdisciplinary group of experts including radiologists, hepatologists, transplant surgeons, and pathologists from United States and international transplant centers and developed new policy recommendations to improve the accuracy of the imaging-based diagnosis of HCC. A prospective trial utilizing these revised guidelines comparing diagnostic performance to pathology at time of transplant is warranted to ensure proper allocation of valuable organs from deceased donors.

2.0 BACKGROUND AND SIGNIFICANCE

The significance of HCC in public health is of two-fold importance, as there is a large at-risk population and increased incidence nationwide. Deceased donor liver transplantation and living donor adult liver transplantation (LDALT) are the best currently available treatment options for HCC. However, patients with ESLD and patients diagnosed with other liver disease compete for the same scarce pool of transplant organs from deceased donors. As all of these conditions are life limiting, the timely assignment of graft livers to the appropriate patients based on individual mortality risk is of vital importance. Additionally, as liver transplantation is associated with significant healthcare expenditure related to postoperative care and long-term immunosuppression therapy, the allocation of transplant livers to unsuitable patients should be avoided for economic reasons.

The presence and severity of ESLD are diagnosed by a combination of clinical and laboratory data, as well as imaging tests and, ultimately, tissue sampling where appropriate. The imaging-based diagnosis of HCC is used to allocate priority on the liver transplant waitlist to those patients who suffer from liver cancer. An expert panel recently developed a draft policy for liver imaging in context with liver transplant allocation in the United States. Minimum technical and protocol requirements, expert interpretation by transplant center radiologists, and a new classification and diagnosis system were created in 2008 in an attempt to increase the specificity of imaging-based liver cancer diagnosis and staging in patients with ESLD. Due to lack of robust clinical data, the proposed policy had to be based on expert consensus rather than scientific evidence generated from clinical trials. It is therefore imperative to test the performance of this new policy in clinical practice to evaluate its impact early on during implementation.

2.1 HCC and Liver Transplantation in the United States

Liver cancer, primarily HCC, is the third leading cause of cancer-related death worldwide and the ninth leading cause of death in the United States. The incidence of HCC has increased by 70% from 1.4 per 100,000 in 1976 to 1980 to 2.4 per 100,000 in 1991 to 1995. Additionally, patients’ age at initial diagnosis has decreased during this period. Still, only a marginal improvement in survival has occurred, with a five-year survival rate of 5%. This poor prognosis is partly due to the advanced tumor stage at time of diagnosis, which precludes effective treatment. Furthermore, the number of HCC cases are expected to increase in the next three decades, as a major risk factor for the development of HCC is another condition increasing in incidence—chronic viral hepatitis B or C.

Liver transplantation for early-stage HCC is more likely to provide a potential cure and has shown improved survival over other less radical techniques. Transplantation is associated with a 75% four-year survival compared to a 25% three-year survival for untreated, small HCCs. HCC was the
primary indication for liver transplantation, which accounted for 18.4% of U.S. liver-transplant recipients in 2007 to 2008. With a rising number of patients in need of liver transplantation and essentially stagnant organ availability, appropriate organ allocation is a growing concern.

The OPTN is the unified transplant network established by the United States Congress under NOTA, established in 1984. UNOS administers the OPTN under contract with the Health Resources and Services Administration of the U.S. Department of Health and Human Services. Current OPTN liver allocation policy is based on objective, verifiable measures of disease severity with minimal emphasis on waiting time. The MELD score predicts survival probability in patients with ESLD. The score is calculated by a formula using routine lab test results. The MELD score is used to tie priority on the transplant waitlist to quantitation of disease severity and, thus, predicted length of survival. In 2002, the U.S. liver transplant allocation system was revised, henceforth granting HCC-exception MELD points to ESLD patients on the transplant waitlist who are diagnosed also with liver cancer and meet the so-called Milan criteria.

2.2 Current Imaging-Based Assignment of Priority and Management of Patients on the Transplantation Waitlist for HCC Diagnosis

A total of 6103 liver transplants were performed in the United States between November 1, 2007, and October 31, 2008. The number of patients transplanted with an approved HCC exception (MELD points assigned for liver cancer diagnosis) was 1293 (21.9%). Of these 1293 patients, the vast majority (n=1143, 88.3%) of diagnoses were based on imaging alone. In 145 patients (11.6%) a combination of biopsy data and imaging findings contributed to the diagnosis. Prerequisite conditions for receiving extra priority for candidates on the waiting list with TNM stage T2 HCC currently include an imaging assessment of the candidate’s liver with ultrasound, computed tomography (CT), or magnetic-resonance imaging (MRI) scan that documents the HCC. Few specific imaging criteria are listed in the current policy, which states that patients must have a “vascular blush corresponding to the area of suspicion seen on the above imaging studies,” or “an arteriogram confirming a tumor, a biopsy confirming HCC, chemoembolization of [the] lesion[s], radiofrequency, cryo-ablation or chemical ablation of the lesion”.

After initial HCC diagnosis, management of patients on the regional transplant waitlists differed significantly: 1287 (54%) out of 2377 individual patients submitted in 2008 for HCC exception had some form of adjuvant local treatment between time of listing and transplantation. Radiofrequency ablation (RFA) accounted for 420 (32.6%); chemoembolization, 966 (75.1%); chemical ablation, 59 (4.6%); cryo-ablation, 4 (0.3%). Some patients underwent multiple types of local adjuvant therapy; for example, 11% of patients had a combination of RFA and chemoembolization.

2.3 Shortcomings of Current Policy

Freeman et al performed a retrospective analysis of the UNOS database comparing the accuracy of radiologic staging with pathologic staging of explant organs in 789 liver transplant recipients. This study found that the performance of MR or CT imaging under the current policy was unacceptable. The imaging data did not portray an accurate staging of the disease, and in many cases resulted in the inappropriate allocation of transplant livers. In 2008, UNOS convened an interdisciplinary group of experts including radiologists, hepatologists, transplant surgeons, and pathologists from the United States and international transplantation centers which developed policy recommendations to improve imaging of HCC. The experts agreed that the current OPTN/UNOS policy requirements were insufficient for imaging-based diagnosis of HCC qualifying the patient for priority on the transplant
waitlist. The current policy contained no technical and protocol requirements for liver imaging and only vague qualitative diagnostic imaging criteria. The inaccurate imaging findings allowed a high number of false-positive diagnoses labeling common benign focal abnormalities in the diseased liver as HCC, resulting in misallocation of donor organs.

2.4 Shortcomings of Imaging After Local Adjuvant Therapy

Imaging criteria for the detection of residual or recurrent tumor after local adjuvant therapy are not well established. The diagnostic accuracy of imaging for the detection of residual or recurrent liver cancer after local ablative therapy has not been formally compared to explant pathology workup in a prospective multicenter trial.

2.5 New Proposed Policy

A new policy for the imaging diagnosis of HCC in context with liver transplant allocation is currently undergoing review in the OPTN/UNOS policy-making process. It incorporates minimum technical requirements for CT and MRI, presents imaging protocol parameters, and proposes a new system for diagnosis, classification, and reporting of liver lesions in this specific clinical context. Apart from introducing a reporting class for technically-inadequate examinations, the new lesion classification was written with the intent to reduce false-positive image diagnoses of liver cancer leading to inappropriate organ allocation. Specific qualitative imaging findings and size criteria were introduced in order to establish the diagnosis of HCC and to set it apart from suspicious lesions not meeting criteria for definitive liver cancer diagnosis (Tables 1 and 2). The performance of the new DRAFT UNOS/OPTN policy will have a significant impact on priority allocation for transplantation based on liver cancer diagnosis.

Performance of the CURRENT UNOS policy was never prospectively assessed in a multicenter study. This older policy lacks standardization of minimum imaging equipment specifications, imaging protocols, and diagnostic criteria across participating institutions. Therefore, it is difficult to quantify the absolute change/improvement to clinical practice expected to occur when the new policy goes into effect. The proposed trial will require uniformity in the imaging approach across numerous institutions and will help define the sensitivities and specificities of the two imaging modalities in this specific clinical context.

It should be noted that when the new DRAFT UNOS/OPTN classification was created, only those imaging features of HCC that were broadly supported by literature and expert consensus were included in the final specific diagnostic criteria. The aim was to simplify and, if anything, increase specificity of the imaging-based HCC diagnosis across clinical practice. However, the trial team recognizes that there may be image observations and considerations beyond mere application of the diagnostic criteria listed in Tables 1 and 2 and Figure 1, which may influence a radiologist’s opinion on whether a nodule represents HCC or not.

Specifically, certain morphologic features of a nodule on CT and, for example, certain appearance of a nodule on T2-weighted or diffusion-weighted MRI may compel the interpreting radiologist to believe that HCC is more or less likely present than they were forced to state simply based on the stringent application on the new UNOS/OPTN criteria. Therefore, in addition to adjudicating a lesion based on the UNOS/OPTN criteria, we will ask that site readers indicate:

- The binary presence of HCC and the probability of HCC on a 0 to 100 point scale; and
• Which imaging sequences aided in these decisions.

This purely observational data shall inform the trial team about patterns of diagnostic consideration in clinical practice and may prove to be useful in modeling potential future sets of criteria by taking into account prevailing clinical practice patterns of the collective readers in the participating centers.

*Tables 1 and 2 and Figure 1 follow on the subsequent pages for easy reference and printing.*
Table 1: Proposed OPTN classification system for liver imaging
(modified for the purpose of this trial by adding sub-category Class 4-g)

<table>
<thead>
<tr>
<th>OPTN Class</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPTN 0</td>
<td>Incomplete or technically inadequate study</td>
<td>Repeat study required for adequate assessment; automatic priority MELD points cannot be assigned based on a OPTN Class 0 classified imaging study</td>
</tr>
<tr>
<td>OPTN 1</td>
<td>No evidence of HCC on good quality, appropriate imaging study</td>
<td>Typically, surveillance would continue according to routine practice at the respective transplant center</td>
</tr>
<tr>
<td>OPTN 2</td>
<td>Benign lesion(s) or diffuse parenchymal abnormality with no dominant focal lesion</td>
<td>Typically, need for any further imaging would be determined on a clinical basis according to routine practice at the respective transplant center (MRI preferred over CT)</td>
</tr>
<tr>
<td>OPTN 3</td>
<td>Abnormal scan, indeterminate focal lesion(s), not currently meeting radiologic criteria for HCC</td>
<td>Typically, follow-up (F/U) imaging would be performed in 6–12 months (MRI preferred over CT)</td>
</tr>
<tr>
<td>OPTN 4</td>
<td>Abnormal scan, intermediate suspicion for HCC; meets some radiologic criteria for HCC - could represent HCC</td>
<td>Consider short term F/U in 3 months (lesions ≥ 2 cm maximum diameter) to 6 months (lesions &lt; 2 cm maximum diameter) with MRI preferred over CT or biopsy. Imaging F/U should be considered if biopsy is negative or not possible</td>
</tr>
<tr>
<td>OPTN 4-g</td>
<td>Abnormal scan, intermediate suspicion for HCC; meets some radiologic criteria for HCC - could represent HCC AND Growth (maximum diameter increase) by 50% or more documented on serial MRI or CT obtained ≤ 6 months apart.</td>
<td>Consider short term F/U in 3 months (lesions ≥ 2 cm maximum diameter) to 6 months (lesions &lt; 2 cm maximum diameter) with MRI preferred over CT or biopsy. Imaging F/U should be considered if biopsy is negative or not possible. Could represent iso- or hypovascular HCC</td>
</tr>
<tr>
<td>OPTN 5</td>
<td>Meets radiologic criteria for HCC</td>
<td>Patient may be eligible for automatic priority MELD points based on this imaging study. Please refer to definitions for Class 5A, 5A-g 5B, 5B-g, and 5T criteria in Table 2</td>
</tr>
</tbody>
</table>
Table 2: Proposed imaging criteria for OPTN Class 5 lesions (compatible with imaging diagnosis of HCC)

<table>
<thead>
<tr>
<th>OPTN Class 5</th>
<th>Lesion Size</th>
<th>Appearance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5A</td>
<td>Maximum diameter of lesion ≥1cm and &lt;2cm, measured on late arterial or portal vein phase images</td>
<td>Increased contrast enhancement on late hepatic arterial phase (relative to hepatic parenchyma)* AND Washout during later contrast phases AND Peripheral rim enhancement (capsule/pseudocapsule) on delayed phase</td>
<td>This category describes a T1 stage HCC which meets stringent qualitative imaging criteria diagnostic of HCC</td>
</tr>
<tr>
<td>OR†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5A-g</td>
<td></td>
<td>Increased contrast enhancement on late arterial phase (relative to hepatic parenchyma) AND Growth (maximum diameter increase) by 50% or more documented on serial MRI or CT obtained ≤6 months apart. Growth criteria do not apply to ablated lesions</td>
<td>A rapidly growing T1 stage HCC with some qualitative imaging features diagnostic of HCC</td>
</tr>
<tr>
<td>5B</td>
<td>Maximum diameter of lesion ≥2cm, measured on late arterial or portal vein phase images.</td>
<td>Increased contrast enhancement on late hepatic arterial images (relative to hepatic parenchyma)* AND Washout‡ on portal venous/delayed phase and/or late capsule or pseudocapsule enhancement</td>
<td>This category describes a T2 stage HCC which meets qualitative imaging criteria diagnostic of HCC</td>
</tr>
<tr>
<td>OR‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5B-g</td>
<td></td>
<td>Increased contrast enhancement on late hepatic arterial images (relative to hepatic parenchyma)* AND Growth (maximum diameter increase) by 50% or more documented on serial MRI or CT obtained ≤6 months apart. Growth criteria do not apply to previously ablated lesions</td>
<td>A rapidly growing T2 stage HCC with some qualitative imaging features diagnostic of HCC Class 5B lesions qualify for automatic HCC-exception MELD points</td>
</tr>
<tr>
<td>5T</td>
<td>Prior local regional treatment for HCC</td>
<td>Past local regional treatment(e.g., TACE or thermal ablation or combination therapy) for HCC (OPTN Class 5 or biopsy-proven prior to ablation)</td>
<td>This category describes residual or recurrent HCC after previous local ablative therapy</td>
</tr>
</tbody>
</table>

* Iso- and hypovascular HCC may occur which do not exhibit this feature, consider biopsy if suspected.
† When faced with a choice between qualitative imaging criteria for cancer versus growth criteria for cancer, the former “trumps” the latter, ie if a lesion has ALL qualitative characteristics for a Class 5B lesion AND meets the growth criteria, it should be classified as 5B. Only use the “–g” growth classes if growth was in fact the decisive factor for classification.
‡ “Washout” is defined as hypointense/hypoattenuating center of lesion compared to background liver parenchyma on portal vein phase and/or equilibrium phase imaging. “Washout” indicates loss of portal vein vascular supply of a lesion compared to background liver parenchyma.
Figure 1. Application of OPTN/UNOS criteria for cirrhosis and focal liver lesion(s)

The flow diagram below illustrates how the above criteria for OPTN/UNOS Classes 4 and 5 lesions applies to patients with underlying hepatic cirrhosis and at least one focal liver lesion.
2.6 Proposed Research

Multiphase contrast-enhanced CT and MRI will be compared to explant pathology liver workup to establish the respective performance characteristics of these imaging modalities to accurately detect, diagnose, and stage hepatocellular cancer in patients with chronic liver disease. The current clinical decision-making relative to the treatment of patients with ESLD depends upon the presence, number, and location of HCC lesions. Thus, our primary approach is to study imaging performance at the lesion level. By comparing these imaging modalities and their interpretation by both local and central readers to the pathological explant results, the proposed research will help identify optimal conditions for the diagnosis and staging of HCC at lesion and patient levels. It is hypothesized that the combination of state-of-the-art multidetector CT or MRI minimum equipment specifications, contemporary multiphase contrast-enhanced imaging protocols, and new diagnostic criteria will reduce false positive image diagnoses of liver cancer and ultimately lead to more informed treatment decisions and appropriate organ allocation and associated priority transplantation in the United States. The diagnostic imaging involved in this particular trial is routine multiphase contrast-enhanced MRI and CT, not to be confused with high-temporal resolution dynamic perfusion MRI or CT. The imaging protocols in this trial can be readily accomplished at UNOS-accredited transplant centers in the United States, which represent the pool of potential enrolling institutions for this trial. This study protocol defines a highly standardized approach to collecting and interpreting cross-sectional images aimed at the detection and evaluation of HCC.

2.7 Specific Hypotheses

1. Modern imaging technology can accurately diagnose and stage HCC in patients with chronic liver disease when performed on state-of-the-art multidetector CT or MRI equipment, with contemporary multiphase contrast-enhanced imaging protocols.

2. Focal liver lesions can be accurately assigned to pre-malignant and malignant diagnostic categories based on patterns of specific imaging findings. The false positive rate in the malignant lesion category can be reduced from current unacceptable levels by utilizing the criteria proposed in the new OPTN/UNOS liver imaging policy.

3. MRI is the superior cross-sectional imaging method for diagnosing HCC in patients with ESLD due to its inherently higher tissue contrast resolution and tissue characterization properties.

4. Imaging with CT or MRI can diagnose residual or recurrent viable HCC after focal ablative therapy in patients listed for liver transplant.

3.0 STUDY OBJECTIVES/SPECIFIC AIMS

3.1 Primary Aim

To compare the sensitivity of multiphase contrast-enhanced CT to that of multiphase contrast-enhanced MR for diagnosing HCC. The primary analysis for this comparison will be performed at the lesion level using core laboratory interpretations of the imaging studies. A secondary analysis will be performed at the patient level.
3.2 Secondary Aims

3.2.1 To compare the positive predictive value (PPV) of CT to that of MRI for diagnosing HCC. The primary analysis for this comparison will be performed at the lesion level using core laboratory interpretations. A secondary analysis will be performed at the patient level;

3.2.2 To compare the lesion-level sensitivity and PPV of CT and MRI as interpreted by radiologists at the respective transplant centers;

3.2.3 To compare the sensitivity and specificity of multiphase contrast-enhanced CT versus MRI for diagnosing residual or recurrent HCC after local ablative therapy in patients listed for liver transplant. The reference standard for this analysis will be based on pathologic diagnosis at time of explantation;

3.2.4 To determine the accuracy of imaging-based diagnosis and staging of HCC in clinical practice using the new OPTN liver imaging criteria compared with the reference standard of pathologic diagnosis and staging at time of explantation;

3.2.5 To explore whether the comparisons of sensitivity and PPV are affected by stratifying patients by AFP level (elevated vs normal).

3.3 Exploratory Aim

3.3.1 To assess the sensitivity and PPV of MRI and CT interpreted at the participating sites on the basis of all available information and sequences and compare to the sensitivity and PPV of the two modalities interpreted using the main study criteria.

4.0 STUDY OVERVIEW

4.1 Enrollment

Patients with ESLD in transplant centers typically undergo routine imaging for detection of HCC. Most centers image these patients with either multiphase contrast-enhanced CT or multiphase contrast-enhanced MRI at least once a year as their standard of care (SOC) imaging. The term “SOC imaging” is used in this trial protocol to describe the imaging modality (MR or CT) that is the “first choice” at a participating institution to diagnose HCC de-novo or update a patient’s HCC-exception MELD points on the liver transplant waitlist every 90-days. If a patient is found to have at least one OPTN Class 5B liver nodule (HCC) on SOC imaging and meets the so-called Milan criteria, this patient may be eligible for listing for liver transplantation with HCC-exception points (either waiting for a liver from a deceased donor to become available or scheduled to undergo an LDALT). Predicated on such enrollment on the OPTN transplant waiting list with HCC-exception points, the patient becomes eligible for participation in the ACRIN 6690 liver imaging study. Patients must be enrolled to the trial within 30 days after OPTN transplant wait listing with HCC-exception points.

This study will enroll a total of 440 participants and will be open to all UNOS accredited liver transplant centers in the United States. The United States is divided currently into 11 transplant regions, which vary in area and number of organ transplant procedures. ACRIN plans to enlist approximately 25 to 30 centers to participate in the study. Using a conservative estimate, recruitment of one participant per month per site would result in 20 participants per month fulfilling our accrual goal of 440 participants within a two-year timeline. This study will not enroll equal numbers from all regions but rather, the quota of participants recruited from a particular UNOS region will be kept proportional to the overall...
contribution of the region to the national total of patients transplanted with HCC-exception points. Historic UNOS data are used to determine the regional quotas. Each site will be notified of their regional accrual as well as the number of sites in their region that will be accruing to the trial.

4.2 Trial Design

After enrollment, the participating center must acquire multiphasic contrast-enhanced imaging with the complementary modality, at the expense of the trial, no later than 30 days after enrollment to the study (if initial diagnosis was made on CT, then MRI or if initial diagnosis was made on MRI, then CT). The term “complementary imaging” is used in this trial protocol for the “other” modality (MR or CT) which will be considered the protocol-required research scan consistently at a center (as opposed to the “SOC imaging, defined in Section 4.1). However, if both MRI and CT scans have already been obtained per protocol on an ACRIN-qualified scanner within 30 days prior to enrollment, neither imaging needs to be repeated; if SOC imaging used for the purpose of UNOS listing is older than 30 days at enrollment, it will need to be repeated at the expense of the trial within 30 days after enrollment, the same time window available for obtaining the complementary imaging. It is acceptable for centers to schedule and obtain both exams on the same day for participant convenience, should the need arise.

Subsequently, participants will undergo SOC and complementary imaging scheduled in accordance with the 90-day intervals required for cyclical update of the HCC-exception points with UNOS. Both CT and MR scans must be completed within 7 days of each other. It is permissible to perform both imaging tests on the same day, preferably in the order CT followed by MRI. The ultimate goal of this imaging schedule is to have a set of images from both imaging modalities available that is 90 or fewer-days-old when transplantation occurs (at a date that is unknown during the wait time period). Results from this last imaging time point prior to transplant will be used for correlation with explant pathology analysis. In the rare event of an unexpectedly early transplantation, the most recent available imaging will be used for correlation with explant analysis, which may result in a time interval longer than 90 days for the complementary modality imaging in a few cases.

4.3 Ablative Therapy and Trial Imaging

If the decision is made that participants should undergo local ablative therapy after transplant listing and enrollment into this study, they will receive both CT and MRI no less than 28 days and no more than 60 days after the last ablative therapy session at the expense of this trial. If several consecutive sessions of transcatheter arterial chemoembolization (TACE) are planned, or combination therapy with TACE and thermal ablation is conducted, participants need to first complete the entire treatment scheme per institutional SOC before undergoing imaging with CT and MRI as described above for post-local ablative therapy. In some participants, the post-ablation imaging time point may coincide with the next serial imaging time point required for liver transplant waitlist updates, in which case only one pair of imaging exams (CT and MR) needs to be obtained, serving both purposes.

Subsequently, these participants continue to be imaged according to the OPTN/UNOS schedule for updating HCC-exception points.

4.4 Expected Drop Out Rates

Historically, the drop-out rate on the transplant waitlist has been approximately 10% for HCC patients. These participants become ineligible for transplant either due to disease progression beyond Milan criteria, becoming “too sick to transplant,” or dying while on the waitlist, either related or unrelated to the HCC. The sample size in this trial has been adjusted to compensate for dropout. Rates of dropout per
region will be monitored. The regional pace of accrual will be adjusted to obtain a nationally-representative study sample should substantial variation across regions be identified during monitoring of the trial. The sample size has been adjusted to account for an expected number of participants who will have no available explant pathology, unless the site successfully obtains a post-mortem liver pathology analysis.

5.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

5.1.1 Must be able to provide a written informed consent;
5.1.2 Must be 18 years or older;
5.1.3 Must have at least one focal liver lesion(s) compatible with imaging diagnosis of T2 stage HCC (OPTN Class 5B liver lesion) on contrast-enhanced CT imaging and/or contrast-enhanced MRI; imaging findings must be within the Milan criteria\textsuperscript{17} (see Appendix V);
5.1.4 Must have been listed on the regional OPTN/UNOS liver transplant waitlist with HCC-exception MELD points within 30 days prior to enrollment in this trial (up-to-date UNOS Policy requirements to determine HCC-exception are available at www.unos.org/policiesandbylaws/policies.asp, see Section 3.6 under Allocation of Livers). Participants listed with the intent to undergo either deceased donor transplant or LDALT are eligible for this trial.

5.2 Exclusion Criteria

5.2.1 Tumors beyond Milan criteria (see Appendix V).\textsuperscript{17} This trial does not enroll patients with tumors beyond Milan criteria even from region(s) where transplant listing might still be permissible due to a special regional arrangement. Any of the following will exclude the patient from the trial:

5.2.1.1 Evidence of extrahepatic tumor;
5.2.1.2 Unifocal HCC > 5 cm in diameter;
5.2.1.3 Multifocal HCCs, 4 or more in number;
5.2.1.4 Multiple (2 or more) HCCs with at least one tumor exceeding 3 cm;

5.2.2 History of having undergone any local ablative therapy to liver prior to enrollment on the trial;

5.2.3 History or current use of sorafenib treatment (or comparable antiangiogenic therapy) prior to enrollment;

5.2.4 Not suitable to undergo MRI with an extracellular gadolinium-based contrast agent that does not have dominant hepatobiliary excretion because of:

5.2.4.1 Claustrophobia;
5.2.4.2 Presence of metallic objects or implanted medical devices in body per institutional safety standards;
5.2.4.3 Sickle cell disease;
5.2.4.4 Weight greater than that allowable by the MR table;
5.2.5 Not suitable to undergo CT with an iodinated contrast agent:

5.2.5.1 Weight greater than that allowable by the CT table;

5.2.6 Renal failure, as determined by estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m\(^2\) by the Modification of Diet in Renal Disease (MDRD) model based on a serum creatinine level obtained within 28 days prior to enrollment;

5.2.7 Renal insufficiency at the time of enrollment, as determined by eGFR 30 to 60 mL/min/1.73 m\(^2\) by the MDRD model based on a serum creatinine level obtained within 28 days prior to enrollment, unless permitted by the institution’s policy and/or American College of Radiology (ACR) guidance for risk reduction strategies (see www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx for guidance on contrast selection and pre-treatment strategies);

5.2.8 Known allergy-like reaction to contrast media (iodinated or extracellular gadolinium that does not have dominant hepatobiliary excretion) or moderate or severe allergic reactions to one or more allergens as defined by the ACR, and unwillingness to undergo pre-treatment as defined by the institution’s policy and/or ACR guidance (see www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx for reaction definition and premedication guidance);

5.2.9 Unable to give informed consent;

5.2.10 Unable to comply with breathing or other imaging related instructions resulting in inability to obtain diagnostic quality CT or MRI studies (OPTN Class 0);

5.2.11 Pregnancy (if a female is of childbearing potential—defined as a premenopausal female capable of becoming pregnant—a pregnancy test should be done).

5.3 Recruitment

The investigative team at each participating site will typically include the radiologist, transplant surgeon, hepatologist and/or oncologist, and pathologist. The site will identify a corresponding site PI who will coordinate efforts at the site and be the primary contact for all site-related matters. We encourage that the site PI be a radiologist (but this is not a requirement) as the cyclical recurring imaging and site reader image interpretations constitute a major portion of the work contributed to this trial. The site PI works closely with the other interdisciplinary members of the site investigative team. Of particular concern for this trial is a close collaboration between the radiology and pathology departments. Direct participation and physical presence of a radiologist at the time of and during the macroscopic explant liver analysis is strongly encouraged to help with identification of the Class 4 and 5 nodules for the purpose of the radiologic-pathologic correlation. This study aims to enroll all suitable participants in a consecutive fashion to exclude any selection bias beyond inclusion/exclusion criteria.

As patients are listed on the OPTN transplant list with HCC-exception MELD points, a review of eligibility criteria will take place. Patients become eligible for enrollment when the diagnosis of at least one HCC (Class 5B lesion) is made on either CT or MRI, and patients are listed for transplant with HCC-exception points. Patients will be approached to participate in the study, ideally as soon as they have been listed for liver transplantation, with HCC exception points, in their respective region.

ACRIN will develop a trial communications plan that will describe the production of materials to aid participant recruitment. All materials used for participant recruitment will be reviewed and approved by each institution’s Institutional Review Board (IRB).
5.4 Inclusion of Women and Minorities
Both men and women and members of all ethnic groups are eligible for this trial. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993, with regard to inclusion of women and minorities in clinical research, the projected gender and minority accruals are shown below:

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hispanic or Latino</td>
<td>17</td>
<td>40</td>
<td>57</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>115</td>
<td>268</td>
<td>383</td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
<td>132</td>
<td>308</td>
<td>440</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Racial Category</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>8</td>
<td>18</td>
<td>26</td>
</tr>
<tr>
<td>Black or African American</td>
<td>15</td>
<td>34</td>
<td>49</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>108</td>
<td>253</td>
<td>361</td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>132</td>
<td>308</td>
<td>440</td>
</tr>
</tbody>
</table>

6.0 SITE SELECTION

6.1 Institution Requirements
The potential sites for this study are ACRIN-participating institutions that meet qualifications for participating in this study. Qualification will include the submission of anonymized, retrospective, multiphase MR and CT liver images from patients with cirrhosis and HCC at each site. Sagittal and coronal reconstructed images derived from the dynamic post-contrast imaging series from both modalities will be required from each site. Each site interested in participation in this trial must submit anonymized DICOM images of three complete exams of each, multiphasic contrast-enhanced CT and MRI, of patients with HCC obtained during the previous 12 months on the scanners intended for use in the trial. The CT and MRI data need not have been obtained in the same patient. If more than one such CT and/or MRI system is anticipated for use in the course of this trial, then qualifying scans for each substantially different vendor/model/platform combination must be submitted. If 1.5T and 3T scanners are to be used for the trial, example images will need to be submitted for both. The images will be reviewed centrally for technical adequacy (timing of contrast enhancement relative to image acquisition, biologic motion, MRI artifacts, etc) and to provide feedback to the site. If the site successfully demonstrates the ability to acquire high-quality liver images, and meets other criteria set forth in this paragraph, the site becomes eligible for participation in the trial.

If several qualified sites from an OPTN/UNOS region apply for participation in this trial, the ACRIN trial team will select sites based on the following criteria:
- Transplant case volume three years prior to application, by year;
- Accreditation by OPTN/UNOS;
- Research track record in (up to four) participating subspecialties in the centers; we will
request bio-sketches from site investigators;
- Letter of commitment from participating departments;
- Occurrence of regular interdisciplinary case conferences featuring HCC/transplant patients at respective institutions.

**NOTE:** This study will not enroll equal numbers from all regions but rather, the quota of participants recruited from a particular UNOS region will be kept proportional to the overall contribution of the region to the national total of patients transplanted with HCC-exception points. The number of sites needed for participation will depend on the regional estimated accrual needed.

Each institution must complete a Protocol Specific Application (PSA) and have the MRI and CT scanners qualified by ACRIN, prior to the institution participating in the study. Detailed information for MRI and CT Qualification Procedures and its application to become qualified, as well as the PSA, can be accessed at [www.acrin.org/6690_protocol.aspx](http://www.acrin.org/6690_protocol.aspx). All regulatory documentation must be submitted to ACRIN Headquarters (via fax: 215-717-0936, ATTN: ACRIN Protocol Development and Regulatory Compliance Department).

### 6.2 IRB Approval and Informed Consent Form

All institutions must have study-specific Institutional Review Board (IRB) approval for the protocol and informed consent form (ICF). The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution. A copy of the IRB approval letter and a copy of the IRB-approved, site-specific ICF must be delivered to the ACRIN Monitor for the trial to review the approved form and to keep on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: Protocol Development and Regulatory Compliance Department) prior to registering the first participant.

### 6.3 Accrual Goals and Monitoring

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 440 participants. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any recruitment barriers. Efforts to increase accrual will be made throughout the trial. The OPTN/UNOS board has recognized this trial as an important collaborative research effort and intends to support planning and execution of this trial by making staff resources and data available to ACRIN as appropriate.

The ACRIN Steering Committee regularly reviews the overall trial accrual and may request information about a trial’s accrual performance to better understand general accrual barriers or issues. Accrual and safety information will be presented to the ACRIN Data and Safety Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the DSMC may, at its discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

### 7.0 DATA MANAGEMENT/ONLINE REGISTRATION

#### 7.1 General

7.1.1 The ACRIN web address is [www.acrin.org](http://www.acrin.org).

7.1.2 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 ACRIN in Philadelphia, PA.

7.1.3 Participant enrollment and data collection occurs 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. 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, the enrolling person should contact the DMC before attempting a re-registration. A DMC contact list is located on the ACRIN web site for each protocol.

7.2 Clinical Data Submission

7.2.1 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 associate (RA) may use the calendar as a case management tool for data submission and follow-up scheduling.

7.2.2 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/alive or until the study is terminated. The case is closed when all data have been received, reviewed, and no outstanding data query exists for the case.

7.2.3 To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, data that are out of range, and data that are in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one
sitting can still be submitted and completed at a later date. The form will remain available on the web until the “Complete Form Submission” button is depressed.

7.2.4 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 are transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

7.2.5 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 ACR can serve as an ISP.

7.3 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.

7.4 Electronic Data Management

7.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Brown BC and the DMC. The logic checks performed on the data at this point are more 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 RA. The validation program generated by BC produces a log of errors, which is sent to the DMC for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC needs to spend resolving problems. Additional data review will take place once the data are 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 BDMC communication with the participating sites is normally done through the DMC.

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

7.5 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 Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool.

7.6 Data Quality Assurance

7.6.1 The 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. 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.

7.6.2 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 PDRC, cannot find a resolution to the problem, it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.

7.6.3 In addition, the ACRIN QA Monitor will review case report forms and source documents at several different time points: after first few participants enrolled and during the conduct of the trial, including staff changes at the participating sites. In addition, the QA Monitor will review the initial and annual regulatory documents and any revised regulatory documents. This monitoring process ensures protocol and regulatory compliance, participant’s welfare and safety, and provides resources to sites for clarification to the protocol and guidance in completion of the case report forms.
8.0 STUDY PROCEDURES
For this study, serial MR and CT imaging will be performed at distinct time points. Timing of serial SOC imaging in waitlisted patients—those eligible for/scheduled to undergo LDALT as well as those waiting for livers from deceased donors to become available—is dictated by OPTN/UNOS HCC-exception point update requirements (90 day intervals). Complementary imaging with the alternate modality will be obtained at baseline within 30 days of enrollment at the expense of the trial to achieve the study objectives. Both SOC and study-related complementary imaging for each participant will need to have been executed per protocol on an ACRIN-qualified scanner within a 60-day period (between 30 days prior to and 30 days after enrollment) and collected at baseline. If SOC imaging used for the purpose of UNOS listing is older than 30 days at enrollment, it will need to be repeated at the expense of the trial within 30 days after enrollment, the same time window available for obtaining the complementary imaging. See Section 8.2 for a description of scenarios for baseline imaging.

Participants with disease staged within Milan criteria who subsequently progress beyond Milan criteria while on trial may be kept in the trial and proceed to explantation under two “special” circumstances: if they happen to either already be living in or be moving to a UNOS/OPTN region that allows listing for deceased donor transplantation at a higher stage and thus may progress to transplant per regional practice OR if the participant is slated to undergo LDALT.

If a participant undergoes local ablative therapy after enrollment, this study protocol requires imaging with both CT and MRI 28 to 60 days after completion of that treatment. Ablative therapy must not be conducted prior to completion of baseline imaging with both modalities nor between serial imaging for the trial (that is, ablation must not occur within the specified 7-day time limit between scans if CT and MR are completed on separate days). If post-ablation imaging coincides with the 90-day HCC-exception point UNOS update cycle, only one set of study-related complementary imaging needs to be obtained. One of the post-ablation imaging studies is considered clinically indicated and will be covered by the participant’s insurance, while the study-related complementary imaging will be performed at the expense of this trial.

SOC and complementary imaging will be performed to support the 90-day intervals required for cyclical update of the HCC-exception points with UNOS. The objective is to have a set of serial images, no older than 90 days prior to transplant in [the majority of] trial participants, available to allow for a comparison of imaging findings with the explant liver pathology findings.

NOTE: All CT and MRI scans should be performed on the same ACRIN-qualified scanners; it is encouraged that the same model scanner should be consistently used for a participant throughout the trial if at all possible.

8.1 Eligibility/Enrollment Visit (Within 30 Days After HCC-Exception Point Liver Transplant Waitlisting)
Patients must be enrolled to participate in the trial within 30 days after being waitlisted with HCC-exception points. At the registration visit, the potential participant will be confirmed for eligibility by the appropriate study-team designee prior to formal electronic enrollment:

8.1.1 Obtain written informed consent from the participant to participate in the trial;
8.1.2 Confirm eligibility which includes:
Review of the inclusion and exclusion criteria, transplantation waitlist status, initial CT and/or MR images, medical history;

Review eGFR levels if assessed 28 days prior to enrollment (if creatinine has not been assessed within 28 days of enrollment, additional laboratory results may need to be obtained to confirm renal status);

8.1.3 Collect data from routine laboratory studies, including basic liver enzyme panel (i.e., aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [AlkPhos], internal normalized ratio [INR], bilirubin, albumin), and alpha fetoprotein (AFP), and assessment for ascites and hepatic encephalopathy;

8.1.4 Confirm images used to determine participant eligibility for transplantation waitlist are available for submission to ACRIN, including, if possible, the most-recent prior MRI and/or CT images; these images may be used as SOC and/or complementary baseline scans OR may need to be repeated if the SOC baseline scan has not been completed per protocol within 30 days of enrollment (see Sections 4.2 and 10.2);

8.1.5 In women of childbearing potential, conduct a pregnancy test as per institution’s SOC. Should a participant become pregnant at any time during the trial, the woman will be off-study;

8.1.6 Enroll patient electronically to the trial via the ACRIN Web site (www.acrin.org).

8.2 Baseline: Initial UNOS Listing Standard-of-Care Imaging Plus Study-Related Complementary Imaging (Within 30 Days After Enrollment)

Both MR and CT images will need to be completed and collected at baseline for all participants; ablative therapy must not be performed prior to completion of these two imaging studies. If both MR and CT scans were completed per protocol on an ACRIN-qualified scanner for initial UNOS waitlist eligibility within 30 days prior to enrollment in the trial, then they may be used as baseline images and no initial study imaging visit will be necessary. Otherwise, SOC and/or complementary imaging will need to be completed per protocol on an ACRIN-qualified scanner within the first 30 days after enrollment if: the SOC scan was completed more than 30 days prior to enrollment, either scan was not performed per protocol on an ACRIN-qualified scanner, and/or the complementary imaging was not performed for initial waitlist assessment. It is acceptable for centers to schedule and obtain both exams on the same day for participant convenience. In that case it is preferable that the CT be performed first, if at all possible.

The following table presented these three possible situations for baseline imaging:

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Within 30 Days PRIOR to Enrollment</th>
<th>ENROLLMENT</th>
<th>Within 30 Days AFTER Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Situation 1</td>
<td>MR and CT images completed (per protocol requirements)</td>
<td></td>
<td>No additional imaging required</td>
</tr>
<tr>
<td>Situation 2</td>
<td>SOC imaging</td>
<td></td>
<td>Complementary imaging completed (if SOC is MR, then complete CT as complementary imaging)</td>
</tr>
<tr>
<td>Situation 3</td>
<td>SOC imaging older than 30 days</td>
<td></td>
<td>BOTH SOC imaging and complementary imaging need to be completed</td>
</tr>
</tbody>
</table>
NOTE: Should a registered participant undergo ablative therapy prior to completion of baseline imaging (both MRI and CT), then the participant will not continue on the trial.

8.2.1 Complementary CT With Iodinated Contrast Agent
- In women of childbearing potential, conduct a pregnancy test per the institution’s SOC; should a participant become pregnant at any time during the trial, the woman will be off-study;
- Evaluate eGFR levels for renal failure only (via participant record review or special testing if necessary) if not assessed within 28 days prior to CT scan;
- Place one (1) IV catheter in the participant’s arm vein to inject the contrast bolus;
- Administer iodinated contrast agent per protocol requirements;
- Perform a multiphase contrast-enhanced CT scan according to requirements outlined in Section 10.0 and online at www.acrin.org/6690_imagingmaterials.aspx;
- Assess for adverse events (AEs) prior to departure from imaging suite; participants will be encouraged to call the research staff to report any adverse reactions.

OR

8.2.2 Complementary MR With Extracellular Gadolinium Contrast Agent Without Dominant Hepatobiliary Excretion
- In women of childbearing potential, conduct a pregnancy test per the institution’s SOC; should a participant become pregnant at any time during the trial, the woman will be off-study;
- Evaluate eGFR levels for renal failure only (via participant record review or special testing if necessary) if not assessed within 28 days prior to MR scan;
- Place one (1) IV catheter in the participant’s arm vein to inject the contrast bolus;
- Administer extracellular gadolinium contrast agent that does not have dominant hepatobiliary excretion per protocol requirements;
- Perform a multiphase contrast-enhanced MR scan according to requirements outlined in Section 10.0 and online at www.acrin.org/6690_imagingmaterials.aspx;
- Assess for AEs prior to departure from imaging suite; participants will be encouraged to call the research staff to report any adverse reactions.

8.3 Study-Related Serial Imaging: Timing Per UNOS Listing Update Requirements (Every 90 Days)
Transplantation centers will perform SOC imaging (CT or MR) to assess disease status and are required to submit the radiologist report (and other clinical information) to UNOS no later than every 90 days for patients to remain on transplant waitlist with updated HCC-exception MELD points. This SOC imaging should occur per customary intervals required by OPTN/UNOS to maintain transplant listing and update HCC-exception points. This trial requires that complement imaging also be completed at approximately the same time SOC imaging is performed; if study-related serial imaging (CT and MRI) cannot be performed the same day, they must be completed within 7 days of each other.
IMPORTANT: Ablative therapy must not interfere with the study-related serial imaging; in other words, centers must not perform elective local ablative therapy between the SOC and complementary imaging, for which a maximum 7-day window is allowable as described below. This should not be a problem since most centers may perform both exams on the same day for participant convenience.

8.3.1 SOC MRI or CT scans will be completed at-least every 90 days per institutional and UNOS listing update requirements to assess participant disease and transplant waitlist status;

8.3.2 Study-related complementary imaging (MRI or CT) will be completed within 7 days of the SOC imaging;

8.3.3 In women of childbearing potential, conduct a pregnancy test per the institutional SOC; should a participant become pregnant at any time during the trial, the woman will be off-study;

8.3.4 Review participant’s basic liver enzyme panel (AST, ALT, AlkPhos, INR, bilirubin, albumin) and serum AFP level;

8.3.5 Review assessment for ascites and hepatic encephalopathy.

NOTE: ALL images obtained with CT and MRI at a specific imaging time point will need to be submitted to ACRIN. This includes all sequences, series, and reconstructions that are completed for participant imaging, e.g., also those MR sequences/images not directly applicable to the criteria used for HCC diagnosis in this trial.

8.4 Post-Ablation Imaging (Re-Imaging 28 to 60 Days After Completed Ablation)

8.4.1 Should a participant undergo local ablative therapy while on the waitlist for liver transplantation (see Section 4.3), biopsy of the ablative area prior to ablation is strongly encouraged, although not mandated of the sites; results of the biopsy must be submitted to ACRIN. Biopsy-based diagnosis of the nodule may be used as a surrogate endpoint in case such a nodule undergoes complete necrosis during ablative therapy and would be considered non-diagnostic during eventual explant pathologic workup;

8.4.2 Additional study imaging will be required within 28 to 60 days after the completion of ablative therapy. Imaging will comprise SOC and study-related complementary imaging, completed within 7 days of each other; as a result, all participants undergoing local ablative therapy will undergo CT and MRI within this timeframe to assess for residual or recurrent HCC;

8.4.3 If no additional ablative therapy is necessary, the participant will return to study-related serial imaging per UNOS listing updates and protocol-specific requirements (see Section 8.3). Should additional ablative therapy be necessary at any time, imaging will be obtained as per Section 8.4;

8.4.4 If several consecutive sessions of transcatheter arterial chemoembolization (TACE) are planned, or combination therapy with TACE and thermal ablation is conducted, participants need to first complete the entire treatment scheme per institutional SOC before imaging with CT and MRI as described above for post-local ablative therapy;
8.4.5 Additional ablation should not be conducted such that it would interfere with the post-ablation imaging (i.e., during the 7-day allowance to complete the post-ablation serial MR and CT imaging).

8.5 OFF-STUDY CRITERIA
- Death without explant pathology analysis and report for submission to ACRIN;
- Removal from the waitlist at any time;
- Renal failure during the trial as defined in Exclusion Criteria Section 5.2.6;
- Ablative therapy prior to completion of baseline imaging (both MRI and CT);
- Changing care facilities to a facility not involved in the trial.
# 8.6 Study Procedures Table

<table>
<thead>
<tr>
<th>Study Procedure</th>
<th>Eligibility/Enrollment (Within 30 Days After Listing with HCC-Exception Points)</th>
<th>Baseline: Initial UNOS Listing SOC Imaging Plus Study-Related Complementary Imaging (Within 30 Days After Trial Enrollment)</th>
<th>Study-Related Serial Imaging‡ (Every 90 Days Per UNOS Listing Update Requirements)</th>
<th>Post-Ablation Imaging (Within 28 to 60 Days After Completed Ablation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent Form</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Review Inclusion/Exclusion Criteria</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Confirm Transplant Waitlist Status</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Review Diagnostic MR and/or CT Images</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Review Medical History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Review Routine Lab Results, Including eGFR Levels</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Review Assessment for Ascites and Hepatic Encephalopathy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Confirm Diagnostic Images Available for Submission to ACRIN*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Conduct Pregnancy Test for Women of Childbearing Potential</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ACRIN Web Registration</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Place IV Catheter for Contrast Bolus</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Inject Contrast (Extracellular Gadolinium Without Dominant Hepatobiliary Excretion for MR or Iodinated for CT)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Standard-of-Care Imaging (MR or CT)†‡</td>
<td>X§</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Study-Related Complementary Imaging (MR or CT)†‡</td>
<td>X§</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Post-Ablation MRI and CT†</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* Institutions are requested to not only upload this baseline imaging study to ACRIN but also the most-recent prior imaging study (same-modality—MR and/or CT), if available.
† All images obtained with CT and MRI at a specific imaging time point will need be submitted to ACRIN. This includes all sequences, series, and reconstructions that are completed for participant imaging.
‡ Each region will image (CT or MRI) a participant approximately every 90 days (or earlier) per the UNOS guidelines. This imaging to evaluate disease is considered standard of care. This research trial requires that complement imaging (CT or MRI, whichever imaging was not done as the standard of care) be completed at each 90-day interval. **This imaging needs to be completed within 7 days of the standard-of-care imaging that was done for that time interval.** It is permissible to perform both imaging tests on the same day, the order of CT prior to MR is preferred.
§ Standard-of-care imaging may be necessary at baseline (at the cost of the trial) if the most recent previous scan was completed more than 30 days prior to participant enrollment. No study-related baseline imaging is necessary if both MR and CT were completed per protocol on an ACRIN-qualified scanner for initial UNOS waitlist eligibility requirements within 30 days prior to trial enrollment and both imaging sets are submitted to ACRIN. Ablative therapy should not be completed between serial CT and MR scans at any time during the trial.
9.0 EXPLANT PATHOLOGY

9.1 Patient Identification

Not all patients transplanted in a participating center will be part of this study cohort. In fact, in most centers, approximately 75% of patients are transplanted with regular MELD points rather than HCC-exception points. Therefore, the majority of explant livers received by a pathology department in a participating center will not belong to a participant from this study cohort. Upon receipt of an explant liver, the local pathologist or a designee familiar with this protocol will check with the transplant team and/or trial study coordinator to see whether the patient is enrolled in this trial so the explant workup can be performed according to the specifications of this trial protocol. Alternatively, the study site investigator and study coordinator will inform the local pathologist of when the study participant went to transplant.

Details of explant pathology processes for correlation with imaging are available in the Pathology Manual online at www.acrin.org/6690_imagingmaterials.aspx. Digital photographs of all relevant macroscopic lesions and each side of all cut gross specimen liver sections will need to be submitted to ACRIN. Submission details are available in the Pathology Manual.

9.2 Explant Liver Workup in Local Pathology Lab

9.2.1 Goals

Of particular concern for this trial is a close collaboration between the radiology and pathology departments. Direct participation and physical presence of a radiologist during the macroscopic explant liver analysis is strongly encouraged to help with identification of the Class 4 and 5 nodules for the purpose of the 1:1 radiologic-pathologic correlation. Availability of the images at time of explant pathology workup is key; this would best be accomplished in respective centers by having either PACS access or other image display available during the organ dissection. Radiologists are familiar with the localization of nodules on imaging, should review the relevant report of Class 4 and 5 nodules in a given participant, and may be able to directly communicate the location of a specific nodule and verify that the correlative tissue sampling at the time of explant pathology workup matches the location of the respective nodule seen on imaging.

9.2.1.1 Identify and sample all OPTN Class 4 and 5 lesions described on imaging and obtain 1:1 macroscopic and histopathologic correlation; summary reports of most recent CT and MRI performed in the participant will be provided to the pathologist by the local site trial designated radiologist and/or the study coordinator. As well, corresponding images will be available through the online trial portal/database and should be reviewed to guide lesion search and 1:1 correlation in the pathology lab;

9.2.1.2 Identify and sample all other suspicious focal liver lesions and report/record those which turn out to be OPTN Class 5 lesions but were not recorded as such (false negative imaging findings);

9.2.1.3 Report pathologic staging on a per patient basis based on Sections 9.2.1.1 and 9.2.1.2 above;

9.2.1.4 Provide macroscopic digital photos of all relevant nodules for correlative purposes;

9.2.1.5 Provide systematic digital macroscopic images of each side of all gross specimen liver slices/sections. Indicate on slices where sampling took place.
10.0 IMAGING PROTOCOL

The protocol-required radiographic images must be in DICOM format on CD/DVD-ROM or submitted via the internet using secure File Transfer Protocol (sFTP), and transmitted along with an Imaging Transmittal Worksheet (ITW) which can be found on the ACRIN 6690 web site (www.acrin.org/6690_imagingmaterials.aspx). The required images must be submitted to the ACRIN Imaging Core Lab. ACRIN can provide electronic image submission and anonymity utilities for participating institutions via TRIAD software. For support in sending the images via the internet using TRIAD, contact the representatives of the ACRIN Image Management Center (IMC) via email at Triad-Support@phila.acr.org or via phone: 215-940-8820.

10.1 Imaging Acquisition

This study will be open to all UNOS-accredited transplantation centers in the United States. Participating centers will need to comply with minimum technical requirements for CT and MR as shown in Tables 4 and 5. Multiphase contrast-enhanced CT and multiphase contrast-enhanced MRI will be used for imaging in this trial. Additional imaging parameter details are available in the ACRIN 6690 Imaging Manual, found online at www.acrin.org/6690_imagingmaterials.aspx. In cases of discrepancy between the protocol and Manual, sites should defer to the Manual contents.

Physical image acquisition may be performed at the participating transplant center or at a different site as long as technical and protocol requirements, including appropriate DICOM-format image submission, are met and the scanners used have been vetted through the ACRIN scanner qualification process for this trial. Interpretation for the purpose of this trial has to be performed according to reporting requirements specified in the protocol by participating transplant center radiologists. If patients listed for transplant with priority points for HCC consent to participate into the study, they will receive the complementary cross-sectional imaging study as part of the trial protocol within 30 days from enrollment, unless both CT and MRI were already acquired initially.

Imaging will then be performed at least every 90 days as per OPTN/UNOS requirement for updating priority MELD points. Under the trial protocol, the study-related complementary modality imaging will occur within 7 days of the interval SOC imaging being completed for assessment of disease while on the waitlist.

All imaging will be transferred to the ACRIN Imaging Core Lab in DICOM format per directions in Section 10.2.

10.1.1 Importance of High-Quality, Carefully Timed Multiphasic Contrast-Enhanced Imaging

It is well known in the imaging community that optimal detection of liver nodules with predominant arterial vascular supply (such as HCC) on cross-sectional imaging (CT or MRI) requires careful timing of image acquisition to take place during late arterial phase of contrast enhancement. At that point in time there is maximal signal-to-background contrast between capillary enhancement in the lesion and surrounding hepatic parenchyma. In most patients, early arterial phase imaging does not improve tumor conspicuity by either quantitative or subjective analysis.\textsuperscript{23,24}
There is a relatively small time window for acquisition of the late arterial phase, which persists for approximately 10 seconds in most patients and explains the need for careful timing.

While also important for diagnostic purposes, the time window of opportunity to acquire images of the hepatic parenchyma during portal vein and equilibrium (delayed) phase is much wider. Therefore it is permissible to use fixed-time delays (approximately 60 to 75 seconds post injection and 120 to 180 seconds post injection) for the later contrast phase imaging. These numbers are suggestions, and portal vein and delayed phase imaging should be performed per institutional preference and standard of care.

10.1.2 CT Imaging

10.1.2.1 General CT imaging parameters are outlined in the table and text below.

- Helical CT scanning is required; axial serial scanning cannot be used.
- Multi-detector scanning must be performed, using a scanner with a minimum of 8 detector rows.
- Pitch should be based on institutional routines. Reconstruction should be performed at $\leq 5$ mm intervals.
- Scanner settings (kV, mAs) should be per institutional routine procedures.
- The use of radiation dose-savings strategies offered on a given scanner platform is encouraged. For instance, dose-modulation should be turned on if available to adapt dose to patient shape throughout the scan. Technologists should pay careful attention to limiting coverage of multiphasic scans to the [anatomic] area of interest.
- Choice of contrast agent should be according to local institutional routine.
- Contrast dose should be 300 mg I/mL or higher concentration, for dose of 1.5 mL/kg body weight.
- Injection rates should be no less than 3 mL/sec of contrast, better 4 to 6 mL/sec. 18G IV is preferred for bolus injection rates.
- Central lines need not be used unless absolutely required due to lack of acceptable peripheral IV access. Central lines should not be used with power injector unless specifically approved for that indication.

10.1.2.2 Abdominal CT

Abdominal imaging should be tailored for multiphase liver imaging techniques. Optional pre-contrast and then late arterial-phase, portal vein phase, and equilibrium/delayed phase post-contrast imaging provides optimal evaluation of the diseased liver for presence of HCC. Each vascular phase scan (expiration preferred) of the liver must be obtained in a single breathhold helical acquisition.

HCC has a range of presentations on CT. The most diagnostic images are the properly timed multi-phase contrast-enhanced images. The following section covers the key elements necessary to achieve optimal diagnostic sensitivity and
specificity, as well as an optional pre-contrast imaging sequence recommended especially after ablative therapy.

10.1.2.3 Guidelines for Multiphasic Contrast-Enhanced CT Imaging

10.1.2.3.1 Pre-contrast: Recommended but not required
Non-contrast imaging through the liver prior to contrast-enhanced imaging is optional and not required for the purpose of this protocol. Note that pre-contrast imaging is recommended for CT studies performed after local ablative therapy, especially after chemoembolization with densely radiopaque materials such as ethiodol. This will help the reader distinguish contrast-enhancing residual or recurrent HCC from radiopaque tissue bound embolization material.

10.1.2.3.2 Late arterial phase
Imaging characteristics include the following:
- Fully enhanced hepatic artery and branches;
- Early contrast enhancement of portal vein;
- Lack of enhancement of the hepatic venous system.

Time to peak enhancement in abdominal aorta at celiac axis level can be determined either by timing bolus injection or through use of triggering facility provided on newer scanners. Some scanners have an “auto-triggering” feature that commences the scan when a pre-defined threshold (typically 100 HU) is reached in the target area; some scanners will display a time-density curve at the pre-defined anatomic location to the technologist and require a manual start of the exam. Either mechanism optimizes timing of the scan to the cardiac output and circulatory time of the individual participant and is strongly preferred over a fixed-time delay exam. Late arterial phase scanning should typically commence 5 to 10 seconds after peak enhancement in the upper abdominal aorta at the level of the celiac axis. In the unlikely event that fixed time delay needs to be used, an empirical delay of 25 to 30 seconds may work for most participants.

10.1.2.3.3 Portal vein phase
Imaging characteristics include the following:
- Fully enhanced portal vein;
- Peak liver parenchymal enhancement;
- Early contrast enhancement of hepatic veins.

The time window of opportunity to acquire images of the hepatic parenchyma during portal vein and equilibrium (delayed) phase is relatively wide. Portal vein phase images should typically be acquired 35 to 55 seconds after initiation of late arterial phase.

10.1.2.3.4 Equilibrium/Delayed phase
Imaging characteristics include the following:
• Variable appearance;
• >120 seconds after initial injection of contrast.

The time window of opportunity to acquire images of the hepatic parenchyma during portal vein and equilibrium (delayed) phase is relatively wide. Equilibrium phase images should typically be acquired 120 to 180 seconds post initial contrast injection.

Table 4: Minimum technical specifications for multiphasic contrast-enhanced CT of the liver

<table>
<thead>
<tr>
<th>Feature</th>
<th>Specification</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanner type</td>
<td>Multidetector row scanner</td>
<td></td>
</tr>
<tr>
<td>Detector type</td>
<td>Minimum of 8 detector rows</td>
<td>Need to be able to image entire liver during brief late arterial phase time window</td>
</tr>
<tr>
<td>Reconstructed slice thickness</td>
<td>Minimum of 5 mm reconstructed slice thickness</td>
<td>Thinner slices are preferable, especially if multiplanar reconstructions are performed</td>
</tr>
<tr>
<td>Injector</td>
<td>Power injector, preferably dual chamber injector with saline flush</td>
<td>Bolus tracking desirable</td>
</tr>
<tr>
<td>Contrast injection rate</td>
<td>No less than 3mL/sec of contrast, better 4–6 mL/sec with at least 300 mg I/mL or higher concentration, for dose of 1.5 mL/kg body weight</td>
<td></td>
</tr>
</tbody>
</table>

Dynamic phases on contrast-enhanced MDCT (comments describe typical hallmark image features)

| 0) OPTIONAL: Pre-contrast | 1) MANDATORY: Late arterial phase | 1) Artery fully enhanced, beginning contrast enhancement of portal vein |
| 2) MANDATORY: Portal venous phase | 2) Portal vein enhanced, peak liver parenchymal enhancement, beginning contrast enhancement of hepatic veins |
| 3) MANDATORY: Delayed phase | 3) Variable appearance, >120 sec after initial injection of contrast |

Dynamic phases (timing) | Bolus tracking preferred over timing bolus for accurate timing |
10.1.3 MR Imaging

10.1.3.1 General MRI parameters are outlined in the table and text below.

- Field strength of 1.5 Tesla or greater.
- Imaging must be performed with a specialized torso array coil or other local coil combinations appropriate for body imaging. Body coil for signal reception is not acceptable.
- Image slice thickness should be $\leq 10$ mm.
- Field of view (FOV) as appropriate for given patient body habitus.
- Matrix for T1 and T2 weighted images should be no less than 256 (frequency) $\times 128$ (phase).
- Diffusion-weighted imaging may be used by sites per institutional protocol but is not required by this trial protocol. If sites perform this type of imaging, the use of lower resolution matrices is acceptable.
- For axial imaging, phase encoding should be anterior–posterior.
- For contrast-enhanced scanning, standard extracellular gadolinium chelates that do not have dominant hepatobiliary excretion should be used at a dose of 0.1 mmol/kg to a maximum of 20 mL.
- Injection rate should be 2 cc/sec, and all injections must be followed by a saline flush of 30 cc. Peripheral IV access is preferred.

10.1.3.2 Abdominal MRI

Contrast-enhanced imaging with a standard extracellular gadolinium chelate that does not have dominant hepatobiliary excretion is required for MRI. Scanning protocol should be per institutional standards, but should include at a minimum: pre-contrast (mandatory) and dynamic post-extracellular-gadolinium T1-weighted (T1W) gradient echo sequence (3D preferable), T2 (with and without FAT SAT), T1W in and out of phase imaging. The inclusion of other imaging techniques/planes is acceptable per institutional/imaging center’s standard, and all imaging performed will be collected for the purpose of this trial.

10.1.3.3 Guidelines for Multiphasic Contrast-Enhanced MR Imaging

HCC has a range of presentations on MRI. The most common is a circumscribed mass that may be inconspicuous on pre-contrast T2W and T1W imaging. The strongest diagnostic images are the multiple contrast-enhanced timed T1W images. The key elements necessary to achieve optimal diagnostic sensitivity and specificity are the following:

- 3D Gradient Echo (GRE) fat-suppressed acquisitions acquired with identical parameters throughout the pre- and post-contrast series. 3D volumetric imaging is preferred, but multiplanar 2D imaging is acceptable.
- Pre-contrast T1W images:
  - 2D or 3D in- and opposed-GRE;
- 3D GRE (depending on scanner platform used: Vibe; Lava-xv; Thrive) with fat suppression.
- Parameters identical to the post-contrast 3D GRE sequence:
  - Avoid misinterpreting a nodule intrinsically with high T1W signal as an enhancing mass, as can be seen in regenerating nodules or dysplasia. HCC rarely has high T1 signal, but can. Comparison must always be made between the pre-contrast and arterial phase images.
  - Examine the in/out-of-phase images for fat. Occasionally the T1 signal may be lower than adjacent liver on fat-suppressed 3D GRE due to lipid, < 10% incidence.

10.1.3.3.1 Pre-contrast: Mandatory
Non-contrast imaging through the liver prior to contrast-enhanced imaging is mandatory.

10.1.3.3.2 Arterial phase
- Imaging characteristics include the following:
  - Fully enhanced hepatic artery and branches;
  - Early contrast enhancement of portal vein;
  - Lack of enhancement of the hepatic venous system.
- Acquisition of a properly timed late arterial phase is the most technically challenging and diagnostically critical element of the dynamic liver examination.
- Both the MRI system and the technologist training must be considered for optimized arterial phase imaging.
- Technologists are reminded to carefully go over patient instructions prior to scanning, especially as they pertain to breathing instructions, to minimize artifact on the study.
- Using set (empirical) timing delays from the start of the injection will be associated with a large range of contrast arrival times (from < 12 to > 30 seconds range timed from the start of the contrast injection to the arrival in the hepatic artery) and will not provide the most optimized method.
- HCC will transiently enhance over a period of 5 to 10 seconds above the adjacent liver parenchyma signal, therefore the timing is critical and is optimized if:
  - The gadolinium bolus is injected in as short a time as possible;
  - Peak HCC enhancement must be aligned in time with the time during the 3D GRE acquisition that accumulates low k-space frequencies (e.g., linear order = align at middle of breath hold; low to high ordering = align at beginning of breath hold, which means adding a longer delay time to account for this).
• The following is required for optimized timing in order to achieve an arterial-phase breath hold liver examination (ABLE):
  o Dual chamber power injector;
  o Injection of contrast at 2 cc/sec (measured to the recommended dose by weight; standard extracellular gadolinium chelates that do not have dominant hepatobiliary excretion should be used at a dose of 0.1 mmol/kg to a maximum of 20 mL);
  o Chase with saline at 2 to 3 cc/sec x 30 cc;
  o Start a real-time reconstruction high–speed, low-quality coronal (suggested) GRE (e.g., care-bolus) at the start of the infusion for bolus monitoring;
  o Field of view on coronal set to allow visualization of the heart, mediastinum, and centered on the diaphragm to visualize the celiac axis;
  o Technologist trained to recognize filling of the right side of heart, pulmonary artery, left heart, aorta, in preparation for recognizing bolus arrival;
  o Stop the bolus imaging and start timing when the contrast arrives at the celiac axis (diaphragm);
  o Count 8 sec if using a linear ordered 16 to 18 sec breath hold acquisition time 3D GRE (based on data looking at perfusion kinetics of arterial enhancing tumors);
  o During this time give the breathing commands and train the technologists to provide adequate time for the participant to complete the breath hold maneuver 2 to 3 sec prior to initiation of the sequence to allow the participant to complete following the command and stop all voluntary movements;
  o Start the arterial phase acquisition.

• An approximate guide to show that an ideal acquisition was obtained usually shows the hepatic artery fully enhanced and the portal veins centrally just enhancing to well enhanced; hepatic veins show no enhancement.

10.1.3.3 Portal venous phase

• Imaging characteristics include the following:
  o Fully enhanced portal vein;
  o Peak liver parenchymal enhancement;
  o Early contrast enhancement of hepatic veins.

• Images captured just after the hepatic veins have filled with contrast. Timing is less critical and can be acquired (35 to 55 sec after initiation of late arterial phase scan). Typically the portal venous phase is started one or two breathing cycles after completion of late arterial phase.
• This provides adequate time for the participant to regain their breath before being asked to perform the next breath hold and reduce motion effects from poor breath holding due to rushing this second enhanced acquisition.
• This acquisition provides optimal visualization for portal or superior mesenteric vein (SMV) thrombosis and varices.

10.1.3.3.4 Equilibrium/Delayed phase
• Imaging characteristics include the following:
  o Variable appearance;
  o >120 seconds after initial injection of contrast.
• Timing less critical and can be acquired at 120 to 180 sec post injection as a third breath hold. This provides adequate time for so-called HCC “wash-out”.
• The signal in the HCC is lower in this phase due to a combination of lower vascular volume and interstitial uptake than in the adjacent liver.
• The margins of the HCC enhance, forming an apparent thin pseudocapsule.

Table 5: Overview technical specifications for multiphase contrast-enhanced MRI of the liver

<table>
<thead>
<tr>
<th>Feature</th>
<th>Specification</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scanner type</td>
<td>1.5 T or greater magnetic field strength</td>
<td>Low-field magnets not suitable</td>
</tr>
<tr>
<td>Coil type</td>
<td>Phased-array multichannel torso coil</td>
<td>Unless patient-related factors precludes use (e.g., body habitus)</td>
</tr>
<tr>
<td>Gradient type</td>
<td>Current generation high speed gradients</td>
<td></td>
</tr>
<tr>
<td>Slice thickness</td>
<td>5 mm or less for dynamic series; 8 mm or less for other imaging</td>
<td></td>
</tr>
<tr>
<td>Injector</td>
<td>Dual chamber power injector recommended</td>
<td>Bolus tracking desirable</td>
</tr>
<tr>
<td>Contrast injection rate</td>
<td>2–3 mL/sec of extracellular gadolinium chelate that does not have dominant hepatobiliary excretion</td>
<td>Preferably resulting in vendor-recommended total dose</td>
</tr>
<tr>
<td>Required non-dynamic sequences</td>
<td>T1W in and out of phase imaging</td>
<td>Optional diffusion imaging</td>
</tr>
</tbody>
</table>
| Dynamic phases on contrast-enhanced MRI (comments describe typical hallmark image features) | 0) MANDATORY:  
Pre-contrast T1W | 0) Do not change scan parameters for post contrast imaging |
|                                       | 1) MANDATORY:  
Late arterial phase                                         | 1) Artery fully enhanced, beginning contrast enhancement of portal vein |
<table>
<thead>
<tr>
<th>Dynamic phases (timing)</th>
<th>The use of a bolus tracking method for timing contrast arrival for late arterial phase imaging is preferable. Portal venous phase (35–55 sec after initiation of late arterial phase scan), equilibrium/delayed phase (120–180 sec after initial contrast injection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breath holding</td>
<td>Max length of series requiring breath hold should be about 20 sec with a minimum matrix of 128 x 256</td>
</tr>
</tbody>
</table>

### 10.2 Images Preparation for Submission

**10.2.1** Removal of Confidential Participant Information: The header record on DICOM formatted image data, which often contains information identifying the participant by name, MUST be scrubbed before the image 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
- Other Participant ID tag with ACRIN Study Number.

**10.2.2** sFTP Transfer: Digitally generated image files in DICOM v3.0 format can be transmitted to the ACRIN core lab via sFTP directly to the image archive. This can be performed using a customized software program or by using TRIAD software available from ACRIN. An Imaging Transmittal Worksheet (ITW) must be faxed at the time images are transmitted. Contact the ACRIN core lab for additional details at **Triad-Support@phila.acr.org**.

**10.2.3** Please fax the ITW to:

ACRIN Core Lab at (215) 923-1737, ATTN: ACRIN 6690 Imaging Specialist

**10.2.4** In the event that the transfer of scrubbed image headers is not available, images may also be sent on a CD/DVD-ROM to the ACRIN core lab for transfer to the image archive. Please contact ACRIN prior to sending the media to confirm compatibility.

**10.2.5** Images and the ITW may be mailed to:

American College of Radiology Imaging Network  
MR/CT Core Laboratory  
Attn: ACRIN 6690  
1818 Market Street 16th floor  
Philadelphia, PA 19103
10.3 Quality Control at ACRIN Core Lab
The ACRIN 6690 protocol explicitly requires participating centers to meet technical specifications for uniformity to the CT and MR scanners used to obtain images. Additionally, specific parameters for image acquisition are outlined in the protocol and provided on the ACRIN website. This routine imaging will occur only at UNOS-accredited transplantation centers that have successfully demonstrated their competence during the site qualification process. ACRIN will provide ongoing quality control through the ACRIN core lab. Specifically, the ACRIN core lab will receive and conduct quality control evaluations on images to help centers maintain trial grade quality. The ACRIN core lab specialists will provide feedback to sites, especially during early trial imaging to ensure high-quality imaging per protocol. However, re-imaging will not be requested once the trial is under way. Furthermore, the protocol contains specific language for image capture (how to scan) and diagnostic (how to read), with specific reporting requirements.

10.4 Provision of Multiplanar (Sagittal or Coronal) Images
As the primary aims of this study necessitate the recognition of borders of liver segments, which are important for lesion localization, axial plane imaging will be mandatory since most readers are most familiar with that imaging plane. Dynamic imaging in the axial plane is customary in most radiology departments. However, the trial team recognizes that (secondary) sagittal or coronal reconstructions may be of value in particular during the radiology-pathology correlation. Primary image acquisition in the sagittal plane may pose challenges due to inherent physics of image acquisition (MRI), possibly increasing likelihood of wrap-around artifacts, etc. The trial protocol therefore asks that sagittal or coronal reconstructions (per preference of local pathologist) of the dynamic images be performed on the scanner consoles or separate 3D workstations. Sagittal and/or coronal images should be provided to ACRIN together with the other required images for each participant. The reconstructed images are made available to the pathologist for correlation at time of explant pathology analysis through institutional PACS or other image display, depending on departmental preference. The quality of such secondary sagittal and coronal reconstructions is expected to be very good when based on isotropic CT data and reasonable when based on (an)isotropic dynamic 3D MRI data.

10.5 Image Interpretation by Local and Central Reader Studies
Image interpretation will be performed by local site radiologists in accordance with new standardized diagnostic class reporting as established by expert consensus at the HCC Consensus Conference, Chicago, IL, 2008 (please refer to Tables 1 and 2, as well as Figure 1, under Section 2.5), which has been adapted for use in this trial. These “local interpretations” will be used to establish the performance of the new diagnostic criteria in clinical practice (“in the field”), as per the study’s Secondary Aim 3.2.4. Local interpreting radiologists also record which modality was used to make the (initial) diagnosis used to obtain priority MELD points. They will record whether prior imaging was available at the time of initial diagnosis and are asked to submit these images to ACRIN since several of the lesion classes are based on growth criteria that can only be accurately assessed in comparison to prior studies.

Lesions will be measured and growth will be assessed based on comparison between most-recent prior imaging (within 90 to 180 days before) and current time point. Prior imaging (180 days and less) must be available at the time of local radiologist assessment.

No more than five (5) Class 4 lesions will be reported for each participant per time point of this trial. Readers are asked to report the five (5) most prominent or most concerning Class 4 nodules. No other specific rules about how to make that determination are dictated; this is left up the best judgment of the
(experienced) reader. Radiologists will be asked to note if and when more than five (5) Class 4 lesions are present. An actual precise count of additional Class 4 lesions will not be reported.

The study-related complement imaging will be interpreted and reported to ACRIN via the data collection forms and, depending on site standard operating procedures, an official radiology report may be furnished. The local site will use the results of this interpretation of the complement imaging for clinical care per the determination and judgment of the transplant team.

All imaging studies will be transferred to the ACRIN core lab, and the matching pair of imaging studies closest in time to the explant date will be interpreted by a minimum of two blinded, expert, central readers. A consensus approach will be used in cases of discrepant expert interpretations, and this consensus diagnosis will be entered into the database. Expert readers also will record image quality and compliance with protocol specifications.

NOTE: Institutions are requested to not only upload this baseline imaging study to ACRIN but also the most-recent prior imaging study (same-modality—MR and/or CT), if available as noted above.

10.6 Reporting of Data
Imaging findings will be recorded on modality-specific (CT and MRI) reader forms on a per lesion basis (reporting every Class 5 lesion and up to five [5] Class 4 lesions). There will be separate, individual reporting required for all OPTN Class 5 lesions (HCC) or OPTN Class 4 lesions (dysplastic nodules, small atypical HCC) by location, size, and specific imaging characteristics. If the participant has undergone prior local ablative therapy, reporting will be done on a per-nodule basis using post-ablation forms for those nodules located in the treated liver (whole liver = all nodules; partly treated liver = some nodules; see Appendix VII for further explanation).

11.0 ADVERSE EVENTS REPORTING
Prompt reporting of AEs is the responsibility of each investigator, clinical RA, and/or nurse engaged in clinical research. Anyone uncertain about whether a particular AE should be reported should contact the ACRIN headquarters at 215-574-3183 for assistance.

Adverse events (AEs) meeting the criteria in the tables below, including all serious adverse events (SAEs) will be reported to the Cancer Imaging Program (CIP) as directed in this section.

AdEERS is an electronic, internet based expedited Adverse Event reporting system operated by NCI/CTEP. It is generally used to capture and disseminate information on relatively significant Adverse Events, based upon trial stage, expectedness, severity, and attribution. However, it may be used to report adverse events of all types if AdEERS reporting is required per protocol.

The electronic-AdEERS AE system is to be used for all ‘expedited reporting’ events as defined herein. If the system is temporarily unavailable, a paper and telephone/FAX based process is provided herein. Expedited AE data is to be re-submitted via the electronic AdEERS system as soon as is possible in cases where temporary e-AdEERS unavailability has necessitated manual capture and submission.
11.1 General Definitions

Adverse Event (AE): For the purpose of this study, an Adverse Event is an untoward medical condition experienced by a study participant during the Adverse Event reporting period defined in Section 11.7 Table A of the protocol, or by applicable guidance, regulation, or policy. An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with participation in the study, regardless of exposure to an agent or procedure, and regardless of whether it is considered to be caused by the agent, device, or process under investigation.

If there is thought to be a conflict between the protocol and a regulatory or guidance source, consult the CIP Clinical Trials Branch. If a decision must be made pending final clarification, the stricter requirement should be applied.

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

Serious Adverse Event (SAE): An SAE is defined as any untoward medical occurrence that meets any one of the following criteria:

- Results in death or is life-threatening at the time of the event
- Requires inpatient hospitalization, or prolongs a hospitalization

NOTE: Hospitalization for expedited AE reporting purposes is a medically required inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should be reserved for situations where the adverse event truly fits this definition, and not for hospitalizations associated with less serious events. For example, a hospital visit where a subject is admitted for observation or minor treatment (e.g., hydration), and released in less than 24 hours, generally is not intended, in and of itself, to qualify as an SAE. Furthermore, hospitalization for pharmacokinetic sampling, is not an AE, and therefore is not to be reported either as a routine AE or in an expedited report. As in all cases, if there is any doubt as to reporting an event, the CIP SAE reporting desk help line is to be consulted promptly.

- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in a participants offspring)

All SAEs are to be followed by the investigator until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology or until subject is lost to follow up.

Adverse Event Expedited Reporting System (AdEERS): AdEERS is a web-based system created by NCI for electronic submission of SERIOUS and/or UNEXPECTED AE reports & is to be used in this study. All CIP trials must use AdEERS for expedited reporting of AEs.

Commercial Agent: A commercial agent is any agent marketed and obtained from a commercial source, and used under approved label indication. For example, the extracellular gadolinium contrast agent without dominant hepatobiliary excretion used in this study is commercial agent.
11.2 AE Reporting Requirements
The list of AEs, and the characteristics of an observed AE [see Section 11.4] will determine whether the event requires expedited (via electronic-AdEERS) reporting in addition to routine reporting. For this study AdEERS reporting will be done electronically.

11.3 Adverse Event List(s) for Study Procedures

11.3.1 Expected Adverse Events Associated With Standard of Care Practice
Any AE that is a result of standard-of-care practice will be reported and managed per the institution’s policies and procedures.

11.3.2 Expected Adverse Events Associated With CT Scan
- Discomfort;
- Claustrophobia.

NOTE: As of July 14, 2008, FDA released a preliminary public health notification of possible malfunction of electronic medical devices caused by CT scanning. Site should use CT scout views to determine if implanted or externally worn electronic medical devices are present and if so, their location relative to the programmed scan range.

11.3.3 Expected Adverse Events Associated With Oral and IV Iodine Contrast
A history of contrast allergy or asthma excludes potential participants from this study unless pre-treated per institutional standard or ACR guidance. The injection may cause discomfort and irritation. The iodine-containing contrast used for CT scanning may cause significant contrast reactions in about one in a thousand participants. Severe reaction is seen in as low as 4/10000 to as high as 2/1000 depending on the type of contrast used. Fatal reactions are exceedingly rare and have been reported in 1:170,000 irrespective of the type of contrast used. The most common reactions are nausea, vomiting, hives, or rash. The risk of death is less than 1 in 10,000.

11.3.4 Expected Adverse Events Associated With MRI
- Anxiety/stress;
- Claustrophobia;
- Discomfort.

11.3.5 Expected Adverse Events Associated With Extracellular Gadolinium Contrast Agent that Does Not Have Dominant Hepatobiliary Excretion
- Nausea;
- Headache;
- Hives;
- Temporary low blood pressure;
- Allergic reaction;
- Rare, but Serious: Kidney impairment, details follow.
Precautions should be exercised for patients with severely impaired renal function or hemolytic anemia. The very unlikely possibility of a reaction, including anaphylactic or cardiovascular reactions, should be considered especially for patients with a known sensitivity to gadolinium or history of asthma.

Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD), kidney disorders, may occur in patients with moderate to end-stage kidney disease (glomerular filtration rate < 30 mL/min/1.73m²) and in patients with renal dysfunction due to the hepatorenal syndrome or in the perioperative liver transplantation period after they have had a MRI scan with extracellular gadolinium-based MR contrast agents (GBMCA) that do not have dominant hepatobiliary excretion.

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

11.3.6 Expected Adverse Events Associated With IV Needle Placement
- Hemorrhage (hematoma at the injection site);
- Plebitis;
- Minor discomfort;
- Bleeding;
- Infection;
- Bruising.

11.3.7 Expected Adverse Events Associated With Radiation Exposure From CT Scan
While the radiation dosage for CT scanning varies with the part of the body being scanned, the exposure (effective dose) for a multiphasic CT of the upper abdomen is typically in the range of 15 to 25 mSv. Actual exposure during a given examination depends on many factors, especially individual patient size; therefore, radiation exposure for these examinations can vary from patient to patient and be smaller or larger than the average dose range provided above. The CT examinations used for this trial are limited to the upper abdomen and typically do not directly irradiate organs with the highest radiosensitivity. However, there is some bone marrow exposure and some exposure to other radiosensitive organs (lung, breast) from scattered radiation.

The total [cumulative] radiation exposure depends on the dose given during any single examination and the number of serial imaging time point update scans required until the patient reaches transplantation. The following table provides individual and cumulative doses broken down by average number of CT examinations expected by UNOS region based on historic data of time from listing to transplant:
Table 6: Single and cumulative dose/exposure ranges for CT examinations during ACRIN 6690

<table>
<thead>
<tr>
<th>Research CT scan time point (total # of CT examinations)</th>
<th>Dose range per exam [mSv]</th>
<th>Cumulative dose range* [mSv]</th>
<th>UNOS region† (based on typical time to transplant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (1)</td>
<td>15–25</td>
<td>15–25</td>
<td>ALL</td>
</tr>
<tr>
<td>90-day update (2)</td>
<td>15–25</td>
<td>30–50</td>
<td>Regions 1, 2, 4, 5, 7, 8, 9</td>
</tr>
<tr>
<td>180-day update (3)</td>
<td>15–25</td>
<td>45–75</td>
<td>Region 1</td>
</tr>
</tbody>
</table>

* If a patient has ablative therapy while on the waitlist, a CT scan is required post-treatment. If this CT scan does not fall in line with the 90-day time points, an additional CT scan will be performed per protocol guidelines. The dose range for this additional CT scan would be equivalent to 15 to 25 mSv.

† Based on historic UNOS data from 2008, the longest time point from HCC-exception point listing to transplant is 208 days across all regions.

Participating sites are strongly encouraged to use all reasonable methods available to lower radiation exposure while maintaining adequate image quality, such as lowering kVp settings in suitably small patients, use of dose modulation technology provided on many scanners, and tight limit on anatomic coverage of the body area of interest.

The maximum exposure expected from a single scan is well below a dose where direct [deterministic] effects of radiation, such as erythema or hair loss, would be observed. Such effects are not expected to occur in this trial. Overall risk from radiation exposure needs to be considered in the clinical context, i.e., the disease a patient is suffering from and the associated limitation in life expectancy. Patients included in this trial typically suffer from advanced-stage chronic liver disease as well as a T2-stage liver cancer. These conditions can significantly limit the patient’s life expectancy, even if transplantation occurs. Based on post-transplant survival data for recipients of deceased donor liver transplants, with an approved T2 HCC exception covering the time period from 2/28/02 to 12/31/08, approximately 32% of patients (approximate 95% confidence interval, 31% to 34%) had died 5 years post-transplant (see Figure 2; data based on personal communication of Dr. Christoph Wald with Erick Edwards (UNOS), 8/20/10).
Considering the significant mortality of the trial patient population, the added lifetime cancer risk to the patient from the radiation exposure in this study would appear to be negligible. It should be noted that the type of CT scanning required for this trial is considered standard of care in many institutions in the United States.

11.4 Adverse Event Characteristics

**Expected Adverse Event:** An expected AE is an event that is listed in the protocol or the Investigator’s Brochure.

**Unexpected Adverse Event:** An unexpected AE is an event that is NOT listed in the protocol or the Investigator’s Brochure.

**Attribution:** Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

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

**Note:** For this study, attributions are in terms of the study related procedures (i.e. study imaging, contrast injection, etc.)
Grade: Grade denotes the severity of the AE. An AE is graded using the following categories:

- Mild
- Moderate
- Severe
- Life-threatening or disabling
- Fatal

NOTE: Severity is graded on a Common Terminology Criteria for Adverse Events (CTCAE) based scale for each CTCAE event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal Hemoglobin values. “Severity” is NOT the same as “Seriousness,” which is an overall assessment that determines reporting requirements.

11.5 CTCAE Term (AE description and grade)
The descriptions and grading scales found in the NCI CTCAE version 4.0 will be utilized for AE reporting. All appropriate clinical areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

11.6 Expedited Adverse Event Reporting
Expedited AE reporting for this study must use electronic AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). Site personnel will be trained in required AE identification and reporting procedures. These requirements are briefly outlined in Table A: Section 11.7 of the protocol.

24 Hour Telephone Reporting Instructions
Any AE/SAEs that require 24-hour notification are reported as follows:

1. CIP– SAE Reporting Line: (301) 897-1704
   - The CIP-SAE reporting line is staffed Monday through Friday from 7:30am – 7:30pm ET (Eastern Time).
   - AE/SAEs may be reported via voicemail during off hours.
   - A TRI contact for AE/SAE reporting will return your call within 24 hours.

   Generally the following details are essential to initiate an AE/SAE report:
   - Name of person reporting the AE/SAE and telephone number
   - Institution name and institution number
   - Protocol title and number
   - Participant’s case number and initials
   - Site principal investigator name and telephone number
   - Date and time of the AE/SAE
   - Date and time you learned of the AE/SAE
   - Brief description of the AE/SAE
   - Site principal investigator’s assignment of the grade of the adverse event
   - Site principal investigator’s assignment of the attribution of the adverse event (do not delay initial report if not available)

2. ACRIN–AE/SAE Reporting Line: (215) 717-2763
The ACRIN–AE/SAE reporting line is monitored by the ACRIN AE Coordinator: Monday through Friday from 8:30am – 4:30pm ET. AE/SAEs may be reported via voicemail during off hours. The ACRIN AE Coordinator will return your call within 24 hours.

Generally the following details are essential to initiate an AE/SAE report:
- Name of person reporting the AE/SAE, telephone number
- Institution name and institution number
- Protocol title and number
- Participant’s case number and initials
- Site principal investigator’s name and telephone number
- Date and time of the AE/SAE
- Date and time you learned of the AE/SAE
- Brief description of the AE/SAE
- Site principal investigator’s assignment of the grade of the adverse event
- Site principal investigator’s assignment of the attribution of the adverse event (do not delay initial report if not available)

IMPORTANT: After the 24 hour contact to CIP and ACRIN-AE/SAE reporting lines, an electronic Adverse Event Expedited Report (AdEERS) must be submitted per the protocol-specific requirements or the regulatory reporting timelines, if not specified in the protocol.

In the rare event that Electronic AdEERS [internet] access is lost, an AdEERS report may be submitted using the following process:

1. Sites should download reporting forms in advance and store them locally for access in the event of internet unavailability. They can be found at:


2. For this study, the Single Agent AdEERS Template will be used.

3. Site completes appropriate sections of the AdEERS report.

   **NOTE:** For events that require 24-hour notification, this is the first step, an AdEERS report is still required within 5 business days.

4. Site faxes the AdEERS report and any additional information (source documents) necessary for thorough review of the event(s) along with the SAE submission form to 301-897-7402, attention CIP SAE Team. The CIP SAE Reporting Desk may be contacted for assistance with any part of this procedure (Tel. 301-897-1704), and should be contacted to confirm receipt of materials sent during any period of AdEERS unavailability, or to provide guidance with the process as appropriate.

5. Site follows up with an email to CIPSAEReporting@tech-res.com notifying the SAE Team that an AdEERS report and additional information (if available) has been faxed.
6. Once AdEERS access is restored, an AE report submitted by the backup process must be entered electronically into AdEERS by the original submitter at the site.

7. AdEERS will be programmed for automatic electronic distribution of reports.

11.7 Expedited Reporting Guidelines

### TABLE A: AdEERS reporting requirements for AEs occurring within 30 Days of the last study procedure

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
<td>Grade 4</td>
<td>Grade 5</td>
</tr>
<tr>
<td>Expected</td>
<td>Expected</td>
<td>Expected</td>
<td>Expected</td>
<td>Expected</td>
</tr>
<tr>
<td>with Hospitalization</td>
<td>without Hospitalization</td>
<td>with Hospitalization</td>
<td>without Hospitalization</td>
<td>with Hospitalization</td>
</tr>
<tr>
<td>Unexpected</td>
<td>Unexpected</td>
<td>Unexpected</td>
<td>Expected</td>
<td></td>
</tr>
<tr>
<td>Unrelated</td>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
</tr>
<tr>
<td>Possible</td>
<td>Probable</td>
<td>Definite</td>
<td>Not Required</td>
<td>Not Required</td>
</tr>
</tbody>
</table>

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

All SAEs are to be followed by the investigator until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology or until subject is lost to follow up.

**Adverse events that occur more than 30 days after the last study procedure and have an attribution of possible, probable, or definite require reporting as follows:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 Unexpected Events

AdEERS 10 calendar day report:
- Grade 3 Unexpected Events with Hospitalization
- Grade 5 Expected Events

1AEs reported through AdEERS must also be reported in routine study data submissions (i.e. ACRIN AE case report form).
2These AEs will require routine reporting (refer to Section 11.9).

11.8 Expedited AE Reporting Timelines Defined:

- “24 hours; 5 calendar days” – The investigator must initially report the AE via a telephone report to NCI/CIP and ACRIN within 24 hours of learning of the event, followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.

- “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.
11.9 Routine Adverse Event Reporting
The following adverse events must be reported in routine study data submissions (i.e. ACRIN AE case report form).

- Grade 3 Expected and Unexpected AEs with an attribution of possible, probable or definite require routine reporting. [See Section 11.7 Table A for AdEERS reporting requirements].
- Grade 4 Expected and Unexpected AEs with an attribution of possible, probable or definite require routine reporting. [See Section 11.7 Table A for AdEERS reporting requirements].
- Grade 5 Expected and Unexpected AEs with an attribution of possible, probable or definite require routine reporting. [See Section 11.7 Table A for AdEERS reporting requirements].

AEs reported through AdEERS must also be reported in routine study data submissions.

11.10 Local Institutional Review Board (IRB) Reporting
Refer to the IRB policies and procedures for AE reporting.

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

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

All study participants in this study will be given an IRB-approved, site-specific ICF describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix 1 for an ICF template). The ICF will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB-approved ICF before the participant is subjected to any study procedures. The approved ICF MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent. Any revisions to the ICF at any time during the trial will need to be submitted to the IRB for approval and submission to ACRIN Protocol Development and Regulatory Compliance Department.

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

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

15.0 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. The investigator will ensure the capability for inspection of all participating sites’ study-related facilities (e.g. imaging centers, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents, and provide adequate space to conduct these visits.

15.1 Monitoring
Monitoring ensures data integrity and quality, as well as that the rights, safety, and well-being of the participants are protected. Monitoring also makes certain that the trial is in compliance with the currently approved protocol/amendments, with GCP and applicable regulatory requirements. It ensures the reported trial data are accurate, complete, and verifiable from source documents. Institutional monitoring will be implemented at several different time points during the conduct of the study. Case report forms (CRFs) and source documents of study participants enrolled at each site will be reviewed. In addition, the initial regulatory documents and any revised regulatory documents will also be monitored.

15.2 Audits
All participating institutions with study participants will be audited. The timing of initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site enrollment), the number of evaluable participants at an individual site, the status of the protocol and pending amendments, and status of the site monitoring.

Generally, audits will be conducted after the number of evaluable participants reaches 20% of targeted accrual, either study-wide and/or at the site level. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate an immediate audit visit. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited which may affect the conduct of the trial. Additionally, site-specific circumstances may prompt an audit visit at any time.

Subsequent audits will be scheduled per the outcome of the initial audit. Audits can be conducted more frequently at the discretion of the protocol team. The audits will be conducted per procedures established by the NCI/CIP. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. CRFs and study-related source documents of study participants enrolled at each
site will be audited. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN and NCI/CIP.

IRB procedures, approvals, and ICFs may also be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org/pdrc.aspx.

To help sites prepare for monitoring and audit visits and to assure that the investigator and the research staff maintain appropriate study-related documents, ACRIN Headquarters will offer training to any participating sites. The training will include all aspects of data collection and special instructions to obtain, file, and maintain the various source documents for verification of submitted trial data. Please refer to the study-specific protocol audit guidelines for details.

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

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

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

15.4 Case Report Forms (CRFs)
CRFs, both web-based and paper forms, 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 on paper CRFs because the procedure was not done or the question was not asked, “N/D” must be noted. If the item is not applicable to the individual case, “N/A” must be noted. All entries on paper CRFs must be printed legibly in black ink on the paper CRFs. In the event of any entry errors, corrections must be made by drawing a single straight line through the incorrect entry, writing the initials of the person making the correction, recording the date when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to ICH Good Clinical Practice Guidelines.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be reviewed against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires must be available for review. Required study image interpretation data that are more detailed in information than the image and not typically documented in the standard radiology report may be documented on the CRF and are acceptable source documentation if signed by the Investigator.
At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date of the exam(s) from the medical record(s). Any use of approved CRFs as source documentation require a signature and date on the CRF with a reference to the information source (participant questionnaire, CT, MR, etc.). Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a major protocol deficiency.

15.5 Institutional Review Board
Sites must obtain initial local IRB approval to participate in ACRIN trials. Prior to participant registration, a copy of the IRB approval letter for the protocol and the ICF must be sent to ACRIN, along with a copy of the IRB-approved, site-specific ICF. Investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

16.0 STATISTICAL CONSIDERATIONS

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REFERENCES


22. Personal communication between Dr. Christoph Wald and Ann Harper of UNOS, March 2009. Documentation on file at ACRIN.


APPENDIX I

ACRIN 6690

SAMPLE CONSENT FOR RESEARCH STUDY

A Prospective, Multicenter Comparison of Multiphase Contrast-Enhanced CT and Multiphase Contrast-Enhanced MRI for Diagnosis of Hepatocellular Carcinoma for Liver Transplant Allocation

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

<<NOTE TO SITES: The following Sample Informed Consent template is designed to be adjusted for the specific needs of your site. Throughout, you will find the language for “<<standard-of-care MR or CT>>” and “<<complementary MR or CT>>”. The complementary imaging is the trial-related imaging scan. Depending on what is standard at your site to determine transplant waitlist status, you will need to adjust this form to ensure that the correct imaging technology appears throughout prior to submitting to your local IRB for review.>>

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

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

You are being asked to be in this liver imaging trial because you have liver disease and are on the waitlist for transplantation.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine and compare how accurate CT (computed tomography) and MRI (magnetic resonance imaging) are in diagnosing liver cancer. For people with liver cancer and other liver disease, the most effective way to treat their disease may be a liver transplant. This research is being done because the study doctors believe they can improve on current methods of placing people with advanced disease on the waitlist for liver transplant. This research intends to show which imaging method gives a clearer picture of liver disease in comparison with the state of the liver when it is removed.

This study is testing two ways of looking inside the body at the liver. The study doctors hope to learn whether images from a CT scan or from an MRI scan provide the best information about liver status. To discover which is better, the images from both the CT and MRI scans will be compared to the actual
liver after it is removed during transplant surgery and examined. With improved imaging methods, the study doctors believe they can better manage the liver transplant waitlist.

About MRI Scans
An MRI uses powerful magnets and radio waves linked to a computer to create cross-sectional images of the body, in this case of the liver. For the MRI scan in this study, a commonly used contrast agent called gadolinium is given to better see certain liver tissues on the MRI images. You will receive the gadolinium contrast agent via a small intravenous (IV) line placed in a vein in your arm.

About CT Scans
A CT scan uses special x-ray equipment to take multiple images from different angles around the body. A computer then processes the information to produce images that show different views of your liver. For the CT scan in this study, a commonly used iodine-based contrast agent is given to better see certain liver tissue on the CT images. You will receive the iodine-based contrast agent via a small IV line placed in a vein in your arm.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
About 440 people will take part in this study from transplant centers across the United States. Approximately 25 to 30 centers will be involved in the study.

HOW LONG WILL I BE IN THE STUDY?
You will be enrolled in the study after you are placed on the waitlist for a liver transplant. You will remain in the study until the time of your transplant or until such time as you are removed from the transplant waitlist for other reasons and are no longer a transplant candidate. The time you are in the study could be from three months to more than two years. This depends on where you live and how long it takes for a donor liver to become available for you.

This study is expected to end after all study participants have had liver transplants, diseased livers have been evaluated after removal, and all the information has been collected. This study may be stopped at any time by your study doctor, ACRIN, Food and Drug Administration (FDA), or National Cancer Institute (NCI) without your consent because:

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

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

You can stop participating at any time. Your decision whether or not to participate in this study will not affect your waitlist status. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your treating doctor first. Withdrawal will not interfere with your future care.

WHAT AM I BEING ASKED TO DO IN THE STUDY?
During the study, you will undergo <<standard-of-care MR or CT>> scans that are typically done at your transplant center to update your transplant waitlist status. The timing of these imaging exams will
be determined by your treating doctor and will depend upon where you live and the availability in your region of livers for transplant. Your study and treating doctors will explain this timing to you.

You may need to have an additional <<standard-of-care MR or CT>> at the beginning of the trial, depending on the timing of the imaging that was used to place you on the transplant waitlist and made you eligible for this trial.

In general, people who have liver cancer and who are waiting for a liver transplant have to undergo imaging every 90 days to check whether their cancer can still be treated with a liver transplant.

For this clinical trial, you will receive <<complementary MR or CT>> scans, one at the beginning of the trial and then repeatedly approximately every 90 days prior to your scheduled transplant. These <<complementary MR or CT>> scans are being done solely for this research trial. You may only have one pair of CT and MRI scans if you go to transplant within a few months of joining the trial. If your wait for transplant is longer, you may have additional pairs of imaging scans.

Imaging taken before the trial that led to your diagnosis, as well as the imaging taken during the trial, will be collected as part of the study so the study doctors can look at all the available information.

**Imaging.** If you take part in this study, you will have the following tests and procedures specific to your participation in this trial:

- At least one (1) <<complementary MR or CT>> scan; you may be asked to complete additional scans depending on your timeline for transplantation.
- If you undergo ablation to your liver (a procedure that may burn or freeze spots where you have liver cancer), you are being asked to undergo MRI and CT scans 28 to 60 days after the treatment is completed. You may be asked to have a biopsy (some tissue removed) of the cancer before the ablation treatment. Obtaining such a biopsy before treating the tumor is routine practice in many institutions to confirm the imaging-based diagnosis of cancer. Typically the biopsy can be obtained through the same access port later used for the ablation procedure.

**Pathology.** When your treating doctors remove your diseased liver, a pathologist (a doctor who defines disease by studying cells and tissue under a microscope) will prepare information from your diseased liver. The study doctors want to compare what is found in your diseased liver that was removed from you with what the imaging studies show. If there are any questions about the results of the pathology review, a sample of the liver tissue may be delivered to ACRIN for further study.

A local pathologist will examine the removed liver. The report from this examination, including images of the pathologist’s work, will be delivered to ACRIN for a later comparison with the results of the MR and CT images. Samples of your removed liver may also be requested by ACRIN for review.

*A Study Chart describing all study procedures follows …*
## STUDY CHART

| Eligibility/Registration | • Sign this informed consent form;  
|                         | • Review of your medical history and lab results;  
|                         | • Have a pregnancy test, if applicable. |

| Initial Study Imaging  
(Within 30 Days After Joining the Trial) | • Have a pregnancy test, if applicable;  
|                                         | • Have your kidney health checked (this may involve a blood test);  
|                                         | • Undergo \(<\text{complementary MR or CT}\)> scan; this will involve getting an intravenous (IV) catheter placed in your arm to receive a contrast agent;  
|                                         | • Possibly undergo \(<\text{standard-of-care MR or CT}\)> if prior imaging was completed more than 30 days before joining the trial. |

| Study-Related Imaging  
at UNOS Listing Updates  
\(<\text{Timing Depends on Site’s Region}>\)  
\(<\text{Most Likely to Be Every 90 Days per UNOS Guidelines}>\) | • Have a pregnancy test, if applicable;  
|                                                             | • Have your kidney health checked (this may involve a blood test);  
|                                                             | • Review of your medical history and lab results;  
|                                                             | • Undergo a CT and an MRI scan; this will involve getting an intravenous (IV) catheter placed in your arm to receive a contrast agent. |

| In the Event that You Receive Ablative  
Liver Therapy …  
Additional MRI and CT Imaging Visit(s)  
(28 to 60 Days After Treatment) | • Have a pregnancy test, if applicable;  
|                                | • Have your kidney health checked (this may involve a blood test);  
|                                | • Undergo a CT and an MRI scan; this will involve getting an intravenous (IV) catheter placed in your arm to receive a contrast agent. |

• Tell the study doctor or research staff if you have any adverse reactions after each of your imaging exams.

## WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?
While on the study, you may be at risk for these side effects. You should discuss these with the research staff and/or your treating doctor. There also may be other side effects that we cannot predict. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the CT or MRI scan is stopped, but in some cases side effects can be serious, long lasting, or permanent.

### Risks Associated With IV Catheter Placement:

*Likely:*
- Minor discomfort;
- Pain in the injection site.

*Less Likely:*
- Bleeding;
- Infection;
Risks Associated With MRI:

Likely:
- Anxiety/stress;
- Claustrophobia;
- Discomfort.

Because of the powerful magnetic force of the MRI scanner, you may not be able to participate in the study if you have:
- Metallic or other surgical implants (for example: pacemaker, heart valves, aneurysm clips, metal plates or pins and some orthopedic prostheses);
- Metal pieces in your eye(s) or other body part(s); or
- Difficulty lying still.

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

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

Risks Associated With Gadolinium:
Approximately two percent (2%) of participants experience some side effects with the use of gadolinium; however, they are mostly mild (nausea, headache, hives, temporary low blood pressure). Serious side effects are very rare and are discussed below.

Less Likely:
- Headaches;
- Nausea.

Less Likely, but Serious:
- Allergic reaction.

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

**Risks Associated With CT Scans:**

*Less Likely*
- Anxiety/stress;
- Discomfort;
- Claustrophobia;
- Rare: Malfunction of worn or implanted electronic medical devices.

If you wear or have electronic medical devices implanted, such as a pacemaker or a drug pump, please make sure you tell your study doctors and research staff. It was recently reported by the FDA that the CT scan may cause the malfunction of electronic medical devices.

**Risks Associated With Radiation Exposure From CT Scans:**

<<SITES: Each site may need to modify this section to quote the correct CT dosimetry for its own CT scanners in accordance with its own institutional policies and procedures.>>

*For example:*

This research study involves a minimum exposure to radiation from 1 diagnostic CT scan. You may undergo additional CT scans depending on your time to transplant. The radiation exposure you will receive from each CT scan is equal to a uniform whole-body exposure of approximately **15 to 25** mSv (a measure of radiation exposure). The total radiation exposure from the minimum number of 1 CT scan is approximately **30 to 50** mSv. For comparison purposes, the allowable annual dose for radiation workers (for example, x-ray technicians) is 50 mSv. Depending on how long you remain on the study, your total radiation exposure may be higher. It depends on the number times you will be scanned before you reach transplantation. The risk from this level of radiation exposure is small when compared with other everyday risks and the potential benefits of these scans during the course of treating your disease.

Here is a table describing how the number of CT scans will affect your radiation exposure. Again, the number of CT scans you will have to have depends on how long it will take for you to receive a liver transplant, and this timing depends on the region where you live.

<<Please adjust the following table to represent the average number of scans for your region (see Section 11.3.7 of the protocol for more detail).>>

<table>
<thead>
<tr>
<th>Average total # of CT examinations in your transplant region &lt;&lt;complete table up to the appropriate average number for your specific region&gt;&gt;</th>
<th>Dose range per exam [mSv]</th>
<th>Cumulative dose range [mSv]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15–25</td>
<td>15–25</td>
</tr>
<tr>
<td>2</td>
<td>15–25</td>
<td>30–50</td>
</tr>
<tr>
<td>3</td>
<td>15–25</td>
<td>45–75</td>
</tr>
</tbody>
</table>

If you would like more information about radiation exposure associated with the CT scans, please speak with your study doctor.

**Risks Associated With the Use of IV Iodine Contrast:**

*Likely:
Discomfort;
Nausea;
Vomiting;
Irritation/hives/rash.

Less Likely, but Serious:
Allergy-like reaction;
Kidney problems (your kidney health will be checked throughout the trial).

Very Rare:
Death. The risk of death is less than 1 in 10,000.

Reproductive Risk
If you are pregnant or nursing or plan to become pregnant during the course of the study, you cannot take part in this research study. Because the CT and MRI scans and contrast agents (dye) used in this study can affect an unborn or nursing baby, you should not become pregnant or breastfeed, or father a baby, while on this study.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THE STUDY?
Taking part in this study is not expected to benefit you directly beyond providing your treating doctors with a particularly thorough look at your liver and its disease with two different types of imaging. However, the knowledge gained from this trial could help doctors to better use imaging to determine who is in greatest need for transplant. We hope the information learned from this study will benefit other patients with liver cancer and other liver disease waiting for transplants in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?
You may choose not to take part in this study. If you choose not to participate, there will be no penalty or loss of benefits to which you are otherwise entitled. You will still undergo <<standard-of-care MR or CT>> per requirements as you await your transplant. Your waitlist status will not be affected. Please talk with your treating doctor about your options.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that your personal information will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. Records of your participation on this study, your progress, and images submitted (such as MRI or CT scans) while you are on the study will be kept in a confidential form at <<Institution>>. Information and images that have eliminated information that can identify you, will be kept in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia.

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

Your research records and images will be kept permanently on file at ACRIN and may be used for future research. It may also be used as the basis for publications by investigators deemed qualified by ACRIN. All data sent to ACRIN over the Internet will be coded so that other people cannot read it. All personal identifiers will be removed and replaced with a unique identifying number to protect your identity. The research that may be done with the information will not specifically help you. But, it might help people who need liver transplants in the future.

**WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?**

Taking part in this study may lead to added costs to you or your insurance company. *<<Standard-of-care MR or CT>>* scans, ablative therapy, and other portions of your care that are considered standard care (that is, if these expenses would have happened even if you were not in the study) are usually covered by most insurance companies, but this is not guaranteed. The study will pay for study-related imaging scans, such as the *<<complementary MR or CT>>* scans, post-ablation MRI and CT scans, or the contrast agents being used for the study. Please ask your study doctor about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

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

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

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. There is no financial compensation that has been set aside to compensate you in the event of injury. The study will not pay for medical treatment.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is your choice. You may choose to take part or not to take part in the study. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you decided to participate, you are free to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not interfere with your future care. You can still get your medical care from our institution.

During the study, we may find out more information that could be important to you. We will tell you about new information or changes in the study that may affect your health or your willingness to continue with the study.

**WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?**

*(This section must be completed)*

This document explains your rights as a study participant. It you have any questions regarding your participation in this research study or you have any questions regarding your rights as a research participant, do not hesitate to speak with your study doctor or anyone listed below.
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, <<insert name>>, at <<insert telephone number>>.

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

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

*(Provide the name of a local IRB contact person)*

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

WHERE ELSE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

You may also visit the NCI’s Web sites for comprehensive clinical trials information, [http://cancertrials.nci.nih.gov](http://cancertrials.nci.nih.gov), or the American College of Radiology Imaging Network web site, [www.acrin.org](http://www.acrin.org).

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. A copy of the signed consent will be given to you.

You willingly give your consent to participate in this study.

<table>
<thead>
<tr>
<th>Printed Name of Study Participant/ Legal Representative</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Printed Name of Person Obtaining Consent</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
</table>

ACRIN 6690 67 September 1, 2010
Supplemental materials that support the conduct of the trial are available on the ACRIN Web site at the ACRIN 6690 Protocol Web page (www.acrin.org/6690_protocol.aspx). Types of materials posted include:

- Application and protocol activation documents (General Qualifying and Protocol Specific Applications, Form FDA 1572, ACRIN Statement of Investigator form, protocol activation checklist, etc.);
- Data forms;
- Imaging materials (Imaging Manual, Image Transmittal Worksheets, Pathology Manual, Pathology Transmittal Worksheet, and scanning and image qualification instructions);
- Recruitment and education materials;
- Regulatory resources;
- Participating site list.

For more information related to the trial, contact the ACRIN 6690 Contact Personnel link on the above-mentioned Web page for a list of protocol team members at ACRIN Headquarters and their roles.
Region 1: CT, MA, ME, NH, RI, VT (eastern)
Region 2: DE, DC, MD, NJ, PA, WV
Region 3: AL, AR, FL, GA, LA, MS, PR
Region 4: OK, TX
Region 5: AZ, CA, NM, NV, UT
Region 6: AK, HI, ID, MT, OR, WA
Region 7: IL, MN, ND, SD, WI
Region 8: CO, KS, IA, MO, NE, WY
Region 9: NY, VT (western)
Region 10: IN, MI, OH
Region 11: KY, NC, SC, TN, VA
## APPENDIX IV

### ACRIN 6690

**OPTN/UNOS: LIVER TRANSPLANTS PERFORMED—BY DIAGNOSIS**  
(U.S. NATIONAL DATA FROM 2007–2008)

OPTN: Organ Procurement and Transplantation Network

http://optn.transplant.hrsa.gov/latestData/ltpL

<table>
<thead>
<tr>
<th>Policy Management</th>
<th>Members</th>
<th>About OPTN</th>
<th>Donation &amp; Transplantation</th>
<th>Data</th>
<th>News</th>
<th>Resources</th>
</tr>
</thead>
</table>

**Transplant : Transplant Year (2007 - 2008) by Diagnosis**

U.S. Transplants Performed : January 1, 1988 - August 31, 2009

For Organ = Liver, Format = Portrait

Based on OPTN data as of November 27, 2009

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<th>Diagnosis</th>
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</thead>
<tbody>
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<tr>
<td></td>
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<tr>
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<td>36</td>
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<tr>
<td></td>
<td>%</td>
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<tr>
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<tr>
<td>Familial Cholestasis: Byle's Disease</td>
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<td>#</td>
</tr>
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<td></td>
<td>%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Familial Cholestasis: Other Specify</td>
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<td>#</td>
</tr>
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<td></td>
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</tr>
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<td>573</td>
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<tr>
<td></td>
<td>%</td>
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<tr>
<td>Graft Vs. Host Dis Sec To Nbh-Li Tx</td>
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<tr>
<td></td>
<td>%</td>
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<tr>
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<td>#</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Meldis: Glyc Stor Dis Type II (Gsd-Iv)</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>1</td>
</tr>
<tr>
<td>Meldis: Hemochromatosis - Hemosiderosis</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>0.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Meldis: Maple Syrup Urine Disease</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

1 of 7

ACRIN 6690

70

September 1, 2010
## APPENDIX IV CON’T

**ACRIN 6690**

**OPTN/UNOS: LIVER TRANSPLANTS PERFORMED—BY DIAGNOSIS**
*(U.S. NATIONAL DATA FROM 2007–2008)*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th># 2008</th>
<th>% 2008</th>
<th># 2007</th>
<th>% 2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meltdis: Other Specify</td>
<td>30</td>
<td>0.1%</td>
<td>30</td>
<td>0.1%</td>
</tr>
<tr>
<td>Meltdis: Primary Orotosis/Oralturia, Hyperoxaturia</td>
<td>9</td>
<td>0.6%</td>
<td>21</td>
<td>0.6%</td>
</tr>
<tr>
<td>Meltdis: Tyrosinemia</td>
<td>1</td>
<td>0.1%</td>
<td>2</td>
<td>0.3%</td>
</tr>
<tr>
<td>Meltdis: Wilson’s Disease, Other Copper Metabolism</td>
<td>34</td>
<td>0.0%</td>
<td>28</td>
<td>0.0%</td>
</tr>
<tr>
<td>Neonatal Cholestatic Liver Disease</td>
<td>0</td>
<td>0.5%</td>
<td>4</td>
<td>0.4%</td>
</tr>
<tr>
<td>Neonatal Hepatitis Other Specify</td>
<td>5</td>
<td>0.1%</td>
<td>7</td>
<td>0.1%</td>
</tr>
<tr>
<td>Prim: Cholangiocarcinoma (Ch-Ca)</td>
<td>41</td>
<td>0.6%</td>
<td>42</td>
<td>0.6%</td>
</tr>
<tr>
<td>Prim: Fibrolamelial (Fi-Hc)</td>
<td>1</td>
<td>0.0%</td>
<td>3</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Data subject to change based on future data submission or correction.
OPTN/UNOS: LIVER TRANSPLANTS PERFORMED—BY DIAGNOSIS
(U.S. NATIONAL DATA FROM 2007–2008)

Transplant: Transplant Year (2007 - 2008) by Diagnosis
U.S. Transplants Performed: January 1, 1988 - August 31, 2009
For Organ = Liver, Format = Portrait
Based on OPTN data as of November 27, 2009

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pmt: Hemangioendothelioma, Hemangiosarcoma, Angio #</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Pmt: Hepatoblastoma (Hbl)</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>%</td>
<td>0.7%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Pmt: Hepatoma (Hcc) And Cirrhosis</td>
<td>917</td>
<td>585</td>
</tr>
<tr>
<td>%</td>
<td>14.5%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Pmt: Hepatoma - Hepatocellular Carcinoma</td>
<td>249</td>
<td>231</td>
</tr>
<tr>
<td>%</td>
<td>3.9%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Pmt: Other Specify (i.e., Kaposi Tumor, Lelormys)</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Primary Biliary Cirrhosis (Pbc)</td>
<td>160</td>
<td>206</td>
</tr>
<tr>
<td>%</td>
<td>2.8%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Psc: Crohn's Disease</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>%</td>
<td>0.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Benign Tumor: Hepatic Adenoma</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Psc: No Bowel Disease</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td>%</td>
<td>1.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Psc: Other Specify</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>%</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Psc: Ulcerative Colitis</td>
<td>108</td>
<td>134</td>
</tr>
<tr>
<td>%</td>
<td>1.7%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Benign Tumor: Other Specify</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Benign Tumor: Polycystic Liver Disease</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>%</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Seo Biliary Cirrhosis: Caroli's Disease</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>
### APPENDIX IV CON’T

**ACRIN 6690**

**OPTN/UNOS: LIVER TRANSPLANTS PERFORMED—BY DIAGNOSIS**  
*(U.S. NATIONAL DATA FROM 2007–2008)*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sec Biliary Cirrhosis: Cholesterol Cyst</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Sec Biliary Cirrhosis: Other Specify</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Secondary Hepatitis: Malignancy Other Specifying</td>
<td>0.5%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Bile Duct Cancer: Cholangioma, Biliary Tract Car</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Biliary Atresia Or Hypoplasia: Other, Specify</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>TTN/Hyperalimentation Ind Liver Disease</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Trauma Other Specify</td>
<td>0.9%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

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### OPTN/UNOS: LIVER TRANSPLANTS PERFORMED—BY DIAGNOSIS (U.S. NATIONAL DATA FROM 2007–2008)

**Transplant Year (2007 - 2008) by Diagnosis**

U.S. Transplants Performed: January 1, 1988 - August 31, 2009
For Organ = Liver, Format = Portrait
Based on OPTN data as of November 27, 2009

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>2006</th>
<th>%</th>
<th>2007</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary Atresia; Extrahepatic</td>
<td>177</td>
<td>0.1%</td>
<td>177</td>
<td>0.1%</td>
</tr>
<tr>
<td>Other, Specify</td>
<td>328</td>
<td>2.6%</td>
<td>414</td>
<td>2.7%</td>
</tr>
<tr>
<td>%</td>
<td>5.2%</td>
<td></td>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>Not Reported</td>
<td>4</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>0.1%</td>
<td></td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>Biliary Hypoplasia; Aplaglie's Syndrome (Paucity)</td>
<td>13</td>
<td>0.2%</td>
<td>13</td>
<td>0.2%</td>
</tr>
<tr>
<td>%</td>
<td>0.7%</td>
<td></td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>Ann: Drug Other Specify</td>
<td>44</td>
<td></td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>0.0%</td>
<td></td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>Biliary Hypoplasia; Nonsyndromic Paucity Of Intra</td>
<td>3</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>0.3%</td>
<td></td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>Budd-Chiari Syndrome</td>
<td>21</td>
<td></td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>0.5%</td>
<td></td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Ann: Etiology Unknown</td>
<td>78</td>
<td></td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>1.2%</td>
<td></td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis Liver Disease; Other Specify</td>
<td>53</td>
<td></td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>0.5%</td>
<td></td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis Autoimmune</td>
<td>139</td>
<td></td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>2.2%</td>
<td></td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis Chronic Active Hepatitis: Etiology Unk</td>
<td>27</td>
<td></td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>0.4%</td>
<td></td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis Cryptogenic (Idiopathic)</td>
<td>327</td>
<td></td>
<td>362</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>5.2%</td>
<td></td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Ann: Other, Specify (E.G., Acute Viral Infection</td>
<td>138</td>
<td></td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>2.2%</td>
<td></td>
<td>2.3%</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX IV CON’T
ACRIN 6690

OPTN/UNOS: LIVER TRANSPLANTS PERFORMED—BY DIAGNOSIS
(U.S. NATIONAL DATA FROM 2007–2008)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>#</th>
<th>%</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis, Cryptogenic- Idiopathic</td>
<td>1</td>
<td>0.0%</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Cirrhosis, Drug/Indust Exposure Other Specify</td>
<td>12</td>
<td>0.2%</td>
<td>10</td>
<td>0.2%</td>
</tr>
<tr>
<td>Cirrhosis, Fatty Liver (Nash)</td>
<td>322</td>
<td>5.1%</td>
<td>295</td>
<td>4.5%</td>
</tr>
<tr>
<td>Cirrhosis, Other, Specify (E.g., Histocytosis, S)</td>
<td>128</td>
<td>10.3%</td>
<td>103</td>
<td>10.3%</td>
</tr>
<tr>
<td>Cirrhosis, Type A</td>
<td>3</td>
<td>2.0%</td>
<td>1</td>
<td>1.6%</td>
</tr>
<tr>
<td>Cirrhosis, Type B And C</td>
<td>22</td>
<td>0.3%</td>
<td>23</td>
<td>0.4%</td>
</tr>
<tr>
<td>Cirrhosis, Type B And D</td>
<td>4</td>
<td>0.1%</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>2008</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis Type B - Hbsag+</td>
<td>109</td>
<td>126</td>
</tr>
<tr>
<td>%</td>
<td>1.7%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Cirrhosis Type C</td>
<td>1,282</td>
<td>1,352</td>
</tr>
<tr>
<td>%</td>
<td>20.3%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Cirrhosis Type D</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Ahn: Type A</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>%</td>
<td>0.1%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Congenital Hepatic Fibrosis</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>%</td>
<td>0.1%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ahn: Type B. And C</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>%</td>
<td>0.0%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Ahn: Type B - Hbsag+</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>%</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

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**Source:** OPTN (Organ Procurement and Transplantation Network) Web site via [http://optn.transplant.hrsa.gov/latestData/step2.asp](http://optn.transplant.hrsa.gov/latestData/step2.asp). These OPTN transplant data were supported in part by Health Resources and Services Administration contract 231-00-0115. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.
The Milan criteria were proposed by Mazzaferro et al\textsuperscript{17} to afford staging of patients with hepatocellular carcinoma (HCC) with the intent to identify those patients at low risk for recurrence after surgical treatment (transplantation) for this disease.

Patients are considered to be within the Milan Criteria with:

- A single HCC \( \leq 5\) cm diameter

OR

- Multiple (3 or less) HCC, each \( \leq 3\) cm in diameter
GFR MDRD CALCULATORS FOR ADULTS (CONVENTIONAL UNITS)

In adults, the best equation for estimating glomerular filtration rate (eGFR) from serum creatinine is the Modification of Diet in Renal Disease (MDRD) Study equation, according to the National Kidney Disease Education Program (a subdivision of the National Institutes of Health). NOTE: This equation should be used only with those creatinine methods that have not been recalibrated to be traceable to isotope dilution mass spectroscopy (IDMS). For more information about recalibration, visit the National Kidney Disease Education Program’s (NKDEP’s) Laboratory Professionals section.

**Original MDRD Study Equation (Conventional Units)**
\[
eGFR \text{ (mL/min/1.73 m}^2) = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American}) \text{ (conventional units)}
\]

**IDMS-Traceable MDRD Study Equation (Conventional Units)**
\[
eGFR \text{ (mL/min/1.73 m}^2) = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African-American})
\]

The equation does not require weight because the results are reported normalized to 1.73 m² body surface area, which is an accepted average adult surface area. This equation should only be used for patients 18 years and older.

**Reduce Rounding Errors**
NKDEP recommends using serum creatinine values in mg/dL to two decimal places (e.g., 0.95 mg/dL) when calculating eGFR using the MDRD Study equation. This practice will reduce rounding errors that may contribute to imprecision in the eGFR value. Values in µmol/L will need to be converted to mg/dL for the purpose of this trial, and both values should be maintained in source documentation.

Source: [www.nkdep.nih.gov/professionals/gfr_calculators/orig_con.htm](http://www.nkdep.nih.gov/professionals/gfr_calculators/orig_con.htm)
Serial Imaging Studies: Standard-of-Care Imaging Per Institutional Norms and Complementary Imaging Per Protocol

A patient will be diagnosed with HCC on an imaging study obtained under a clinical indication (CT or MRI per institutional preference). If disease is within Milan criteria, the patient becomes eligible for listing on liver transplant waitlist with HCC-exception MELD points. If the patient then is enrolled in the ACRIN 6690 study, complementary imaging with a second imaging modality is then obtained under the study protocol. This pair of serial imaging studies (CT and MRI) is considered the baseline exam. Ablative treatment must not occur between enrollment and completion of both baseline imaging exams nor between MR and CT during baseline or serial imaging scans.

Subsequently imaging with both modalities will occur within <90-day intervals to obtain updated HCC-exception MELD points for the participant per UNOS/OPTN guidelines. Centers are welcome to schedule the exam with both modalities on the same day for participant convenience. On the ACRIN case report form used to report technical assessment and imaging findings to ACRIN, the next UNOS listing update time point for HCC-exception points should be selected, e.g. the next serial imaging pair after baseline would be the 90-day time point, then 180-day time point, etc. Readers will be provided with a calendar that can be used to identify which UNOS listing update time points have already been obtained so they may select the appropriate time point label for the study at hand.

Post-Ablation Imaging

Under this protocol, serial imaging with both CT and MRI is required within 28 to 60 days after completion of any local ablative therapy. If both TACE and thermal ablation are planned in a participant, imaging should occur 28 to 60 days after the last treatment step has been completed. On both, the CT and MRI ACRIN case report forms associated with this time point, post-ablation should be selected on the form to classify the imaging event appropriately.

The post-ablation imaging may be so close to the next required UNOS listing update time point that the center would like to use the imaging for this purpose. If this is not known at the time of post-ablation imaging, it will be communicated to the trial team by the transplant coordinator when the decision has been made, and the data reported on the post-ablation ACRIN case report form will be associated with the next scheduled UNOS listing update time point.

Reporting Lesions

All Class 5 lesions will be identified, reported on ACRIN case report forms, and defined as treated or untreated lesions (see details below). Readers also are asked to report the five (5) “most prominent” or “most concerning” Class 4 lesions. No other hard rules are dictated about how to make that determination; this is left up the best judgment of the (experienced) reader. The reader will not be required to fill out a detailed lesion reporting form for more than five (5) Class 4 lesions; rather, the ACRIN case report form requires the reader to document the fact that more than five (5) Class 4 lesions are present without an exact count.
Readers do not report benign nodules and benign liver lesions such as hemangiomas, focal nodular hyperplasia (FNH), adenomas, shunts, cysts, etc., on the ACRIN case report forms (i.e., no OPTN/UNOS Class 1 to 3 lesions are recorded for the purpose of this trial).

**Reporting of “Untreated” and “Treated” Lesions**

Untreated lesions are reported on a per-lesion basis on the ACRIN case report form for untreated lesions. Please answer all questions on the form and classify the lesions according to the scheme provided. Again, reporting of lesions should NOT include unequivocally benign lesions such as cysts, shunts, hemangiomas, etc. Based on the diagnostic criteria used on this trial lesions are either classified as cancer (Class 5) or non-cancer (Class 4) with the appropriate modifiers for growth, etc.

If a participant has undergone TACE, all lesions in the treatment field are considered treated lesions and are reported on the corresponding ACRIN case report form. This is independent from their actual appearance, which is reported on the form with common features as on the untreated lesions form. Any Class 5 lesion that has been treated will be classified as 5T (T=treatment) at that time and going forward.

If a participant has undergone unilobar TACE then all lesions in the treated lobe are to be reported as treated lesions on the appropriate form, and those in the contralateral lobe are considered untreated lesions and are to be reported on the appropriate form.

Depending on the kind of therapy that was administered, a single participant could require the reporting of treated and untreated lesions. If only local thermal ablative therapy (but no TACE) was administered, obviously only the treated nodule(s) would be considered treated and all others untreated.

**Defining Presence of HCC for a Given Lesion**

Readers will indicate the presence HCC by answering a binary yes/no question. In addition, readers will give the probability of the presence of HCC in a 100 point scale. A score of 100 indicates that cancer is definitely present and a score of 0 indicates that cancer is definitely not present.

In analogy, the trial asks readers to determine whether there is residual/recurrent cancer present immediately after local ablative therapy has been completed and on subsequent studies. Again, readers will indicate the presence of HCC in a binary yes/no question and a 100 point scale.