PennState

HRP-591 - Protocol for
Human Subject Research

Protocol Title:

Provide the full title of the study as listed in item 1 on the "Basic Information" page in CATS IRB (http://irb.psu.edu).

Accuracy of Contrast-Enhanced Ultrasound for Hepatocellular Carcinoma (HCC) Post Transcatheter Arterial Chemoembolization (TACE)

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Version Date:

Provide the date of this submission. This date must be updated each time the submission is provided to the IRB office with revisions. DO NOT revise the version date in the footer of this document.

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Clinicaltrials.gov Registration #:

Provide the registration number for this study, if applicable. See "HRP-103- Investigator Manual, When do I have to register my project at ClinicalTrials.gov?" for more information.

NCT04569799

Table of Contents

1.0 Objectives

1.1 Study Objectives

Describe the purpose, specific aims or objectives. State the hypotheses to be tested.

In this study, we propose a prospective trial to determine if contrast enhanced ultrasound (CEUS) is non-inferior to CT or MRI in patients with hepatocellular carcinoma (HCC) following transcatheter arterial chemoembolization (TACE) treatments, in a U.S. population, using Lumason contrast agent. This would be the largest trial to date examining this patient population in the U.S.

The primary objective of our study is to estimate the sensitivity and specificity of the CEUS (Research Timepoint 1) and evaluate for non-inferiority between CEUS and the clinical gold standard of CT/MRI using the Liver Reporting & Data System (LIRAD). We will be assessing the presence of treated or residual tumor, new sites of disease, and portal vein thrombus. Patient factors, such as BMI, underlying liver disease type, alpha fetoprotein level, and size of liver will be recorded. If findings of metastatic disease external to the liver are identified on CT or MRI and not seen on CEUS, they will be recorded.
CEUS, like regular ultrasound, only images specific organs and cannot identify necessarily metastatic disease, as ultrasound cannot image bones and lungs for this purpose.

The second objective of the project will compare the CEUS with a second, standard of care, follow-up CT or MRI (performed 2-4 months later [Research Timepoint 2]). CT can have false negatives due to ethiodol obscuring subtle, early disease and it is possible that CEUS could identify residual disease earlier compared to the gold standards, but would be characterized as a false positive if compared only to the initial imaging (Timepoint 1). This follow-up will evaluate for false positives or negatives on any of the modalities.

The third objective of the project will evaluate patient subjective data in regards to imaging modality preference and possible effects on compliance. The survey will be administered at the conclusion of Timepoint 1 and will include questions about anxiety, comfort, compliance, and modality preference, graded on a Likert scale.

1.2 Primary Study Endpoints

State the primary endpoints to be measured in the study.

Clinical trials typically have a primary objective or endpoint. Additional objectives and endpoints are secondary. The endpoints (or outcomes), determined for each study subject, are the quantitative measurements required by the objectives. Measuring the selected endpoints is the goal of a trial (examples: response rate and survival).

- Non-inferiority between CEUS and the patient's routine CT/MRI, which occurs 2-4 months after TACE treatment (Research timepoint 1). Additionally endpoints that will be measured include treated, residual, or new tumor present on the follow-up.
- The second routine follow-up of CT/MRI (timepoint 2) will be compared to exclude false positives/negatives in the first follow-up imaging (timepoint 1), which occurs approximately 2-months after the first imaging visit.
- Patient subjective data – through the use of a patient survey, given after the first follow-up (Research timepoint 1), where patient had CEUS and CT/MRI (2-4 months after TACE treatment.

1.3 Secondary Study Endpoints

State the secondary endpoints to be measured in the study.

To determine if patient or tumor characteristics (BMI, pre-treatment alpha feta protein levels, size of tumor treated) are predictive of whether CEUS is non-inferior to CT/MRI or in which cases it may not be, due to the limitations of ultrasound as a modality.

2.0 Background

2.1 Scientific Background and Gaps

Describe the scientific background and gaps in current knowledge.

For clinical research studies being conducted at Penn State Health/Penn State College of Medicine, and for other non-PSH locations as applicable, describe the treatment/procedure that is considered standard of care (i.e., indicate how patients would be treated in non-investigational setting); and if applicable, indicate if the study procedure is available to patient without taking part in the study.

Contrast-enhanced ultrasound (CEUS) has been in use globally for decades, but has only recently been approved for clinical use in the U.S. The accuracy of CEUS is similar to MRI and CT scans in establishing the diagnosis of hepatocellular carcinoma (HCC) in at risk-patients (1) and is being utilized with greater frequency to make this important diagnosis in patients with cirrhosis in the U.S.

One of several treatments for HCC is transcatheter arterial chemoembolization (TACE), with follow-up in 2-4 months - typically with either a CT or MRI. The efficacy of CEUS in the post-TACE HCC population has been evaluated in the literature (2-14) , which shows that it is reliable in diagnosing this entity via CEUS. However, some of the articles are with contrast agents not available in the US, some are in different patient populations than is common in the US (for example, hepatitis B is less common in the US than alcoholic cirrhosis, but the converse is true in most of the references studies, which were performed internationally) and should be replicated in the US population, and many of the articles were retrospective.

Over the last few years there has been slowly growing literature available in the U.S. patient population, in the form of case reports (15) or small (fewer than 20 patients) prospective studies (16, 17). But even these studies are not comparable with current CEUS practices, as both Shaw and Nam's small studies used Definity, a contrast agent approved in the U.S. that has low, but higher adverse events than Lumason (18) contrast agent, which is the standard contrast that is utilized at Penn State Milton S. Hershey Medical Center. And so there is a need for larger prospective studies utilizing Lumason in the more obese U.S. population.

2.2 Previous Data

Describe any relevant preliminary data.

In unpublished work (CATS IRB STUDY00014728) presented at the 2019 Society of Radiologists in Ultrasound annual national meeting, our group presented on our experience in imaging liver patients with CEUS (19). At the time of presentation, 62 patients had been imaged, with 16% yielding a positive finding. Our group correctly diagnosed all lesions – all malignant lesions and vascular thrombi had confirmation via gold standard imaging of CT or MRI, or on explanation; benign lesions were confirmed by stability on follow-up imaging. Our study also evaluated patient factors that resulted in limited visualization with CEUS, which included severe steatosis and/or increased abdominal adiposity. In addition, at our institution, we have utilized CEUS in several patients post-TACE, which were subsequently shown to correctly diagnosis residual tumor by follow-up MRI and/or TACE (unpublished). If one were able to accurately and reliably use CEUS to determine residual tumor after TACE, this would decrease the need for CT scans (which have the risk of radiation and contrast-enhanced nephropathy) and MRI scans (which are very expensive and are difficult to perform in patients with claustrophobia).

2.3 Study Rationale

Provide the scientific rationale for the research.

These studies referenced above are not directly applicable to modern CEUS that is performed in the U.S. for the following reasons: 1) the contrast agents used in several studies are different from those available in the U.S. (2, 9, 13, 14) and 2) several of the studies are at least a decade old, and during the last ten years there have been advances in ultrasound imaging quality (10-14). In addition, many of the studies included small sample sizes, with fewer than 30 patients enrolled in the studies (5, 8, 10, 12, 14). Additionally, these results may not be generalizable to the U.S. patient population, as the vast majority of the prospective studies that directly compared CEUS to MRI or CT looked at patient populations outside of the U.S. (2-14). Worldwide (and particularly in Asia where most of these studies have been done), Hepatitis B is the most common etiology of cirrhosis and HCC, but in the U.S. this is not a common etiology. In the U.S. there are more patients with fatty liver disease, which has implications for affecting the accuracy and quality of the CEUS given the increased abdominal adiposity. In addition, with different etiologies of cirrhosis, the patients that develop HCC may have different tumor biology. HCC identification has been proven in the U.S. literature, but evaluation of HCC post TACE treatment has not in robust trials.

If CEUS is demonstrated to be non-inferior to MRI or CT, its use could result in overall cost savings to the patient and healthcare system, decreased radiation exposure, and decreased risk of contrast induced nephropathy from iodinated contrast agents. Ultrasound is significantly less expensive than MRI or CT, and does not expose patients to radiation as in the four phase CT required in screening for HCC. MRI requires screening to ensure safety of entering the scanning room, due to the strong magnetization that is utilized in generating images, and cannot be utilized in patients with pacemakers or automated implantable cardioverter defibrillators (AICDs), which are becoming more prevalent in our aging population. The bore of the magnet is small and patients may suffer issues with claustrophobia, which are not concerns in CEUS. Patient comfort may also be improved as the consistent breath hold required for CT and MRI to be diagnostic is not necessary in CEUS. The contrast used in ultrasound has a safer risk profile than CT dye (18, 20, 21) and severe contrast reactions are rare with ultrasound-based contrast agents. Long term deposition of MRI contrast in the brain has been reported in patients, and the lasting effects of this are currently unknown (22). Additionally, ultrasound contrast is not excreted through the kidneys, so renal function or risk of subsequent renal damage is not of concern. There will also be further decreases in the hidden costs of CT scan and MRI as it is standard of care to check a serum creatinine prior to a CT scan or MRI, and if the creatinine is elevated, there will be a need for intravenous hydration before and after the exam.

3.0 Inclusion and Exclusion Criteria

Create a numbered list below in sections 3.1 and 3.2 of criteria subjects must meet to be eligible for study enrollment (e.g., age, gender, diagnosis, etc.).

Vulnerable Populations:

Indicate specifically whether you will include any of the following vulnerable populations in this research. You MAY NOT include members of these populations as subjects in your research unless you indicate this in your inclusion criteria because specific regulations apply to studies that involve vulnerable populations.

The checklists referenced below outline the determinations to be made by the IRB when reviewing research involving these populations. Review the checklists as these will help to inform your responses throughout the remainder of the protocol.

- **Children –**Review "HRP-416- Checklist - Children"
- **Pregnant Women** – Review "HRP-412- Checklist - Pregnant Women"
- **Cognitively Impaired Adults-** Review "HRP-417- Checklist - Cognitively Impaired Adults"
- **Prisoners-** Review "HRP-415- Checklist - Prisoners"
- **Neonates of uncertain viability or non-viable neonates-** Review "HRP-413- Checklist - Non-Viable Neonates" or "HRP-414- Checklist - Neonates of Uncertain Viability"

3.1 Inclusion Criteria

Create a numbered list of the inclusion criteria that define who will be included in your final study sample (e.g., age, gender, condition, etc.)

1. Adult (≥18 years of age) patients with diagnosed HCC, who are treated with their first round of TACE.
2. Sex: male or female
3. BMI ≤ 40

3.2 Exclusion Criteria

Create a numbered list of the exclusion criteria that define who will be excluded in your study.

1. Children (<18)
2. Patients who do not speak English
3. Patients with a history of hypersensitivity reactions to sulfur hexafluoride lipid microsphere components or to any of the inactive ingredients in Lumason.
4. Patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias)
5. Patients who have a prior non-contrast ultrasound, within last 3 months (at time of consent), where the tumor could not be seen – most commonly due to severe steatosis or obesity.
6. Pregnant or nursing woman
7. Patients who do not plan to get their follow-up CT/MRI at Hershey Medical Center.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Insert subject withdrawal criteria (e.g., safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.).

Patients who are successfully enrolled in the study at the time of TACE will be excluded if the treated lesion is not visible on the grayscale ultrasound at timepoint 1, and contrast would therefore not be administered.

Additionally, if patients do not return for their scheduled CT/MRI, following TACE treatment, they will be removed from the study.

3.3.2 Follow-up for withdrawn subjects

Describe when and how to withdraw subjects from the study; the type and timing of the data to be collected for withdrawal of subjects; whether and how subjects are to be replaced; the follow-up for subjects withdrawn from investigational treatment.

Not applicable

4.0 Recruitment Methods

- Upload recruitment materials for your study in CATS IRB (http://irb.psu.edu). **DO NOT** include the actual recruitment wording in this protocol.
- StudyFinder: If StudyFinder (http://studyfinder.psu.edu) is to be used for recruitment purposes, separate recruitment documents do not need to be uploaded in CATS IRB. The necessary information will be captured from the StudyFinder page in your CATS IRB study.
- Any eligibility screening questions (verbal/phone scripts, email, etc.) used when contacting potential participants must be uploaded to your study in CATS IRB (http://irb.psu.edu).

4.1 Identification of subjects

Describe the source of subjects and the methods that will be used to identify potential subjects (e.g., organizational listservs, established recruitment databases, subject pools, medical or school records, interactions during a clinic visit, etc.). If not recruiting subjects directly (e.g., database query for eligible records or samples) state what will be queried, how and by whom.

StudyFinder:

- If you intend to use StudyFinder (http://studyfinder.psu.edu) for recruitment purposes, include this method in this section.
- Information provided in this protocol needs to be consistent with information provided on the StudyFinder page in your CATS IRB study.

For Penn State Health submissions using Enterprise Information Management (EIM) for recruitment, and for non-Hershey locations as applicable, attach your EIM Design Specification form on in CATS IRB (http://irb.psu.edu). See "HRP-103- Investigator Manual, What is appropriate for study recruitment?" for additional information. **DO NOT** include the actual recruitment material or wording in this protocol.

All patients at Penn State Hershey Medical Center who have a TACE ordered by a referring clinician will be identified as potential subjects. Opportunities for enrollment occur at the clinician office if one of the sub-PIs is treating the patient, and also within the Cardiovascular Interventional Radiology (CVIR) suite, where all patients are treated for TACE. All applicable patients will be approached at one of those times for enrollment.

4.2 Recruitment process

Describe how potential subjects first learn about this research opportunity or indicate as not applicable if subjects will not be prospectively recruited to participant in the research. Subject recruitment can involve various methods (e.g., approaching potential subjects in person, contacting potential subjects via email, letters, telephone, ResearchMatch, or advertising to a general public via flyers, websites, StudyFinder, newspaper, television, and radio etc.). **DO NOT** include the actual recruitment material or wording in this protocol.

4.2.1 How potential subjects will be recruited.

Potential subjects will be recruited during a clinic visit, if seen by a sub-PI, or at the time of their TACE treatment in the CVIR. A screening checklist will be used by the consenting physician to ensure eligibility. Information on the screening checklist will be gleaned from the patient's medical record and/or information collected from the TACE consent.

4.2.2 Where potential subjects will be recruited.

Recruitment may occur in the clinicians' office visit if conducted by one of the sub-investigators, or within the CVIR suite, at the time of their TACE treatment. Subjects will be enrolled in either the clinical visit room or in the dedicated Image-guided Procedure Unit in the Department of Radiology.

4.2.3 When potential subjects will be recruited.

Subjects will be recruited during their clinicians' office visit, if conducted by one of the sub-investigators, or at the time of consent for their standard-of-care TACE procedure.

4.2.4 Describe the eligibility screening process and indicate whether the screening process will occur before or after obtaining informed consent. Screening begins when the investigator obtains information about or from a prospective participant in order to determine their eligibility. In some studies, these procedures may not take place unless HIPAA Authorization is obtained OR a waiver of HIPAA Authorization when applicable for the screening procedures is approved by the IRB. [*For FDA regulated studies, consent for any screening activities would need to be obtained prior to screening unless specifically waived by the IRB.]*

The eligibility screening process will occur after obtaining informed consent for the research. Information on the screening checklist will be gleaned from the patient's medical record and/or information collected from the TACE consent.

5.0 Consent Process and Documentation

Refer to the following materials:

- The "HRP-090- SOP - Informed Consent Process for Research" outlines the process for obtaining informed consent.
- The "HRP-091– SOP - Written Documentation of Consent" describes how the consent process will be documented.
- The "HRP-314- Worksheet - Criteria for Approval" section 7 lists the required elements of consent.
- The "HRP-312- Worksheet - Exemption Determination" includes information on requirements for the consent process for exempt research. In addition, the CATS IRB Library contains consent guidance and templates for exempt research.
- The CATS IRB library contains various consent templates for expedited or full review research that are designed to include the required information.
- Add the consent document(s) to your study in CATS IRB (http://irb.psu.edu). Links to Penn State's consent templates are available in the same location where they are uploaded. **DO NOT** include the actual consent wording in this protocol.

5.1 Consent Process:

Check all applicable boxes below:

☒ **Informed consent will be sought and documented with a written consent form *[Complete Sections 5.2 and 5.6]***

☐ **Implied or verbal consent will be obtained – subjects will not sign a consent form (waiver of written documentation of consent) *[Complete Sections 5.2, 5.3 and 5.6]***

☐ **Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception). *[Complete section 5.2, 5.4 and 5.6]***

☐ **Informed consent will not be obtained – request to completely waive the informed consent requirement. *[Complete Section 5.5]***

The following checkbox is for all locations EXCEPT Penn State Health and College of Medicine:

☐ **Exempt Research at all Locations Except Penn State Health and the College of Medicine: If you believe that the research activities outlined meet one or more of the criteria outlined in "HRP-312-**

Worksheet- Exemption Determination." Please verify by checking this box that if conducting an exempt research study, the consent process will disclose the following (all of which are included in "HRP-590- Consent Guidance for Exempt Research"):

Penn State affiliation; name and contact information for the researcher and advisor (if the researcher is a student); the activities involve research; the procedures to be performed; participation is voluntary; that there are adequate provisions to maintain the privacy interests of subjects and the confidentiality of the data; and subjects may choose not to answer specific questions.

If the research includes the use of student educational records include the following language in this section (otherwise delete): The parent or eligible student will provide a signed and dated written consent that discloses: the records that may be disclosed; the purpose of the disclosure; the party or class of parties to whom the disclosure may be made; if a parent or adult student requests, the school will provide him or her with a copy of the records disclosed; if the parent of a student who is not an adult so requests, the school will provide the student with a copy of the records disclosed.

Note: If this box has been checked, skip the remainder of section 5 and proceed to section 6 of this protocol. If the investigator's assessment is inaccurate, an IRB Analyst will request revision to the protocol and that an informed consent form be submitted for review and approval. Except for exemptions where Limited IRB Review (see "HRP-312- Worksheet- Exemption Determination") is required or where otherwise requested by the IRB, informed consent forms for research activities determined to be exempt without Limited IRB Review are generally not required to be submitted for review and approval by the University Park IRB.

5.2 Obtaining Informed Consent

5.2.1 Timing and Location of Consent

Describe where and when the consent process will take place.

Informed consent will be obtained in one of two places. If a potential subject is seen by one of the sub investigators during a clinicians' office visit, the subject will be consented at that time. Alternatively, potential subjects will be consented in the CVIR suite at Hershey Medical Center where TACE is performed.

5.2.2 Coercion or Undue Influence during Consent

Describe the steps that will be taken to minimize the possibility of coercion or undue influence in the consent process.

Subjects will be informed that participation is voluntary and that their decision will not affect their care. A physician study team member will discuss the study with the patients, review the consent, and answer all questions. Subjects can opt out prior to receiving their CEUS.

5.3 Waiver of Written Documentation of Consent

Review "HRP – 411 – Checklist – Waiver of Written Documentation of Consent."

5.3.1 Indicate which of the following conditions applies to this research:

☐ The research presents no more that minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

OR

☐ The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject

will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. (*Note: This condition is not applicable for FDA-regulated research. If this category is chosen, include copies of a consent form and /or parental permission form for participants who want written documentation linking them to the research.)*

OR

☐ If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained. (*Note: This condition is not applicable for FDA-regulated research.)*

Describe the alternative mechanism for documenting that informed consent was obtained:

Not applicable

5.3.2 Indicate what materials, if any, will be used to inform potential subjects about the research (e.g., a letter accompanying a questionnaire, verbal script, implied consent form, or summary explanation of the research)

5.4 Informed consent will be sought but some of the elements of informed consent will be omitted or altered (e.g., deception).

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.4.1 Indicate the elements of informed consent to be omitted or altered

Not applicable

5.4.2 Indicate why the research could not practicably be carried out without the omission or alteration of consent elements

Not applicable

5.4.3 Describe why the research involves no more than minimal risk to subjects.

Not applicable

5.4.4 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

Not applicable

5.4.5 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

Not applicable

5.4.6 Debriefing

Explain whether and how subjects will be debriefed after participation in the study. If subjects will not be debriefed, provide a justification for not doing so. Add any debriefing materials to the study in CATS IRB.

Not applicable

5.5 Informed consent will not be obtained – request to completely waive the informed consent requirement

Review "HRP-410-Checklist -Waiver or Alteration of Consent Process" to ensure that you have provided sufficient information.

5.5.1 Indicate why the research could not practicably be carried out without the waiver of consent

Not applicable

5.5.2 Describe why the research involves no more than minimal risk to subjects.

Not applicable

5.5.3 Describe why the alteration/omission will not adversely affect the rights and welfare of subjects.

Not applicable

5.5.4 If the research involves using identifiable private information or identifiable biospecimens, describe why the research could not be practicably be carried out without using such information or biospecimens in an identifiable format.

Not applicable

5.5.5 Additional pertinent information after participation

Explain if subjects will be provided with additional pertinent information after participation. If not applicable, indicate "not applicable."

Not applicable

5.6 Consent – Other Considerations

5.6.1 Non-English-Speaking Subjects

Indicate what language(s) other than English are understood by prospective subjects or representatives.

If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Indicate whether the consent process will be documented in writing with the long form of the consent documentation or with the short form of the consent documentation. Review "HRP-091 –SOP- Written Documentation of Consent" and "HRP-103 -Investigator Manual" to ensure that you have provided sufficient information.

Not applicable

5.6.2 Cognitively Impaired Adults

Refer "HRP-417 -CHECKLIST- Cognitively Impaired Adults" for information about research involving cognitively impaired adults as subjects.

5.6.2.1 Capability of Providing Consent

Describe the process to determine whether an individual is capable of consent.

Not applicable.

5.6.2.2 Adults Unable to Consent

Describe whether and how informed consent will be obtained from the legally authorized representative. Describe who will be allowed to provide informed consent. Describe the process used to determine these individual's authority to consent to research.

For research conducted in the state of Pennsylvania, review "HRP-013 -SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "legally authorized representative."

For research conducted outside of the state of Pennsylvania, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "children" in "HRP-013 - SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable.

5.6.2.3 Assent of Adults Unable to Consent

Describe the process for assent of the subjects. Indicate whether assent will be required of all, some or none of the subjects. If some, indicate which subjects will be required to assent and which will not.

If assent will not be obtained from some or all subjects, provide an explanation of why not.

Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.

Not applicable.

5.6.3 Subjects who are not yet adults (infants, children, teenagers)

5.6.3.1 Parental Permission

Describe whether and how parental permission will be obtained. If permission will be obtained from individuals other than parents, describe who will be allowed to provide permission. Describe the process used to determine these individual's authority to consent to each child's general medical care.

For research conducted in the state of Pennsylvania, review "HRP-013-SOP- Legally Authorized Representatives, Children and Guardians" to be aware of which individuals in the state of Pennsylvania meet the definition of "children."

For research conducted outside of the state of Pennsylvania, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along with

the definition of "children" in "HRP-013-SOP- Legally Authorized Representatives, Children, and Guardians."

Not applicable

5.6.3.2 Assent of subjects who are not yet adults

Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent. When assent of children is obtained describe whether and how it will be documented.

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

This section is about the access, use or disclosure of Protected Health Information (PHI). PHI is individually identifiable health information (i.e., health information containing one or more 18 identifiers) that is transmitted or maintained in any form or medium by a Covered Entity or its Business Associate. A Covered Entity is a health plan, a health care clearinghouse or health care provider who transmits health information in electronic form. See "HRP-103 -Investigator Manual" for a list of the 18 identifiers.

If requesting a waiver/alteration of HIPAA authorization, complete sections 6.2 and 6.3 in addition to section 6.1. The Privacy Rule permits waivers (or alterations) of authorization if the research meets certain conditions. Include only information that will be accessed with the waiver/alteration.

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Include the following statement as written – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable</u>.**

Not applicable

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Describe the plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research. Include when and how identifiers will be destroyed. If identifiers will be retained, provide the legal, health or research justification for retaining the identifiers.

Not applicable

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Provide an explanation for why the research could not practicably be conducted without access to and use of PHI.

Not applicable

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Provide an explanation for why the research could not practicably be conducted without the waiver or alternation of authorization.

Not applicable

6.3 Waiver or alteration of authorization statements of agreement

By submitting this study for review with a waiver of authorization, you agree to the following statement – DO NOT ALTER OR DELETE unless this section is not applicable because the research does not involve a waiver or alteration of authorization. **If the section is <u>not</u> applicable, <u>remove</u> the statement and <u>indicate as not applicable.</u>**

Not applicable

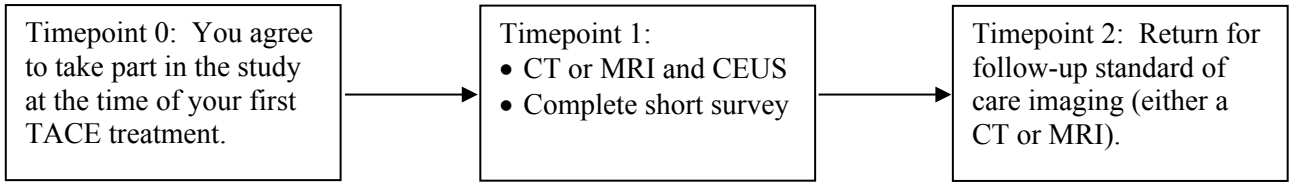
7.0 Study Design and Procedures

Data collection materials that will be seen or used by subjects in your study must be uploaded to CATS IRB (http://irb.psu.edu). **DO NOT** include any actual data collection materials in this protocol (e.g., actual survey or interview questions)

7.1 Study Design

Describe and explain the study design.

This is a prospective trial to determine if contrast enhanced ultrasound (CEUS) is non-inferior to CT or MRI in patients with hepatocellular carcinoma (HCC) following transcatheter arterial chemoembolization (TACE) treatments. All patients will receive standard of care CT/MRI and will also get a contrast ultrasound to directly compare.



7.2 Study Procedures

Provide a step by step description of all research procedures being conducted (broken down by visit, if applicable) including such information as below (where and when applicable); describe the following:

- HOW: (e.g., data collection via interviews, focus groups, forms such as surveys and questionnaires, medical/school records, audio/video/digital recordings, photographs, EKG procedures, MRI, mobile devices such as electronic tablets/cell phones, observations, collection of specimens, experimental drug/device testing, manipulation of behavior/use of deception, computer games, etc.)
- WHERE: (e.g., classrooms, labs, internet/online, places of business, medical settings, public spaces, etc.)

Subject demographics, disease state, and tumor characteristics, CT/MRI and CEUS results will be recorded and entered in REDCAP and Oncore.

7.2.1 Timepoint 0

Provide a description of what procedures will be performed on visit 1 or day 1 or pre-test in order of how these will be done. If your study only involves one session or visit, use this section only and indicate 7.2.2 as not applicable.

Our proposed study population includes subjects with diagnosed HCC, who are treated with TACE. Patients will be identified and enrolled at the time of initial TACE.

7.2.2 Timepoint 1

Provide a description of what procedures will be performed on visit 2 or day 2 or post-test in order of how these will be done. If your study involves more than two sessions or visits replicate this section for each additional session or visit (e.g., 7.2.3, 7.2.4, etc.).

Following initial TACE, patients will receive a CT or MRI, as routinely ordered in the post-TACE setting, to assess for residual or new HCC. The timing of this follow-up occurrence will be followed as routinely ordered by the patients' providers and not be decided upon or affected by involvement in the trial. At this same imaging follow-up visit, patients will also receive a one-time additional contrast-enhanced ultrasound (CEUS). This visit will be performed at either the main hospital or our East Campus, depending on availability and patient needs. MRI, CT, and CEUS will be completed at the same location (i.e., both CT/MRI & CEUS will be completed at either the main hospital or East campus), allowing patient convenience and privacy to simply move between rooms for both exams.

The CEUS will be performed and interpreted by a single radiologist, who is blinded to the CT/MRI, but not to the original tumor site and any prior images. A similarly blinded second radiologist will provide a second read of the CEUS to ensure accuracy at a later date. The same radiologists will be responsible for performing each task for research purposes and will both be members of the research study team. Results from the CEUS will not generate a formal report in the electronic medical record, but will be used only for the research study and entered into REDCAP. The CT or MRI will be interpreted formally by a clinical radiologist, and be dictated and entered into the electronic medical record as standard of practice, outside of the scope of this study. The patient will be administered a short survey about the modalities at the conclusion of their exams utilizing grading on a Likert scale.

7.2.3 Timepoint 2

Per standard clinical care, patients typically return for repeat imaging (CT/MRI) within 2-4 months following the first imaging visit. The decision for follow-up timing is not part of the study, but is decided upon by their clinical physicians. The results of these studies will be included in our data analysis, but no additional intervention will occur at this time.

7.3 Duration of Participation

Describe how long subjects will be involved in this research study. Include the number of sessions and the duration of each session - consider the total number of minutes, hours, days, months, years, etc.

Total duration of participation will be approximately 4 months. Active participation is only required during their initial post TACE treatment imaging visit and the imaging performed 2-4 months post TACE treatment.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Provide a brief description of all test articles (drugs (including any foods and dietary supplements), devices and/or biologics used in the research including the purpose of their use and their approval status with the Food and Drug Administration (FDA). Include information about the form of the drug product (e.g., tablets, capsules, liquid).

Contrast enhanced ultrasound utilizes standard ultrasound units with a contrast software package included on the machine. The test utilizes Lumason (Bracco), which comes in a sterile vial as a powder. It is reconstituted at the time of use with sterile saline (provided in the Lumason package). Each kit provides the equivalent of two liver doses (2.4 mL each). The reconstituted liquid Lumason is then injected intravenously, followed by a flush with sterile saline (5-10 mL saline after each Lumason dose). Lumason is FDA approved for liver lesion evaluation in adults, which is what this study is evaluating (specifically, liver lesions in patients with hepatocellular carcinoma after treatment). After TACE treatment, the liver lesion may shrink, but does not entirely disappear, so contrast ultrasound will be evaluating the residual lesion that is left – is there residual viable tumor left, or not.

7.4.2 Treatment Regimen

Describe dose, route of administration and treatment duration. Include information about dose adjustments.

Intravenous injection of Lumason, 2.4 mL dose (standard liver dose, FDA approved), followed by saline flush. Each vial of Lumason comes with two doses included. This will be administered as in standard of practice of the radiology department at Penn State Health.

7.4.3 Method for Assigning Subject to Treatment Groups

Describe the randomization process and how the associated treatment assignment will be made.

All subjects will receive the CEUS.

7.4.4 Subject Compliance Monitoring

Insert the procedures for monitoring subject compliance.

PI will provide oversite by monitoring data monthly for enrollment, adverse events.

7.4.5 Blinding of the Test Article

Describe how the test article is blinded.

Not applicable

7.4.6 Receiving, Storage, Dispensing and Return

Lumason will be used per the FDA label and as standard of care in the radiology department at Penn State Health

7.4.6.1 Receipt of Test Article

Describe how the test article will be obtained and from what source. Describe how the study test article will be packaged along with amounts (e.g., number of tablets/capsules or volume of liquid) and labeling. If drug kits are used, describe all the contents of the kit and associated labeling.

Not applicable.

7.4.6.2 Storage

Describe the plans to store, handle the test article so they will be used only on subjects and only by authorized investigators. Describe storage temperature requirements and how temperature will be monitored and recorded.

Not applicable.

7.4.6.3 Preparation and Dispensing

Describe how the test article will be assigned to each subject and dispensed. Describe the steps necessary to prepare the test article. Include where the test article preparation will be done and by whom. Fully describe how the study treatment is to be administered and by whom.

Not applicable.

7.4.6.4 Return or Destruction of the Test Article

Describe the procedures for final reconciliation of the test article supply at the end of the study and whether the test article is to be shipped back to a source or destroyed on site.

Not applicable

7.4.6.5 Prior and Concomitant Therapy

Describe what prior and/or concomitant medical therapy will be collected. Describe which concomitant medicines/therapies are permitted during the study. Describe which concomitant medicines are not permitted during the study.

No limitations on other medications patients may take.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Indicate the maximum number of subjects to be accrued/enrolled. Distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures if applicable (i.e., numbers of subjects excluding screen failures.)

We plan to enroll 34 subjects.

8.2 Sample size determination

If applicable, provide a justification of the sample size outlined in section 8.1 to include reflections on, or calculations of, the power of the study.

Planned sample size = 34

Presently there is no data available to suggest how large an effect size may exert on the primary outcome measures. Accordingly, a formal sample size calculation was not done as the goal of this pilot study is to: 1) assess the feasibility of the study design, 2) generate data needed for a formal power calculation, and 3) generate pilot data for larger-scale grant submission. Based on the availability of patients, feasibility of our operations, we plan to recruit 34 patients. We believe this sample will serve our purpose well as a pilot study with plans to include further patients as funding allows.

8.3 Statistical methods

Describe the statistical methods (or non-statistical methods of analysis) that will be employed.

Patient demographics and major clinical information described above will be summarized using descriptive statistics. The main outcome variables in primary objective are the incidence of residual tumor and new tumor, which are both binary. The rate of residual/new tumors using CEUS and CT/MRI will be compared using McNemar's test, which is suitable for comparing paired binary variables. The point estimate and 95% confidence interval (CI) of the incidence rate for CEUS and CT/MRI will be reported separately. Due to the limited sample size of this pilot study, the non-inferiority between CEUS vs CT/MRI will be evaluated just by comparing the CIs of the incidence rate for each method, not by a formal statistical non-inferiority test which requires a much larger sample size. A few additional sub-group analyses will be performed to see if the incidence rate varies by stratification (such as BMI group, liver disease type). Due to the exploratory nature of this study no multiple regression models will be used, and no adjustment of the alpha rate will be made due to multiple testing. Treating the CT/MRI as the clinical gold standard, the sensitivity and specificity of CEUS will be estimated with their 95% CIs. The data from secondary objective will be analyzed similarly as those for the primary objective. For tertiary objective, the subjective ratings from patients between the CT/MRI and ultrasound will be compared using nonparametric Wilcoxon Signed-rank tests. The ratings may be further correlated with some of the baseline demographic and clinical factors using nonparametric Kruskal-Wallis tests. All analyses will be performed using statistical software SAS version 9.4 or higher (SAS Institute, Cary, NC, USA). All tests are two-sided and the significance level to be used is 0.05.

9.0 Data and Safety Monitoring Plan

This section is required when research involves more than Minimal Risk to subjects as defined in "HRP-001 SOP- Definitions."

Minimal Risk is defined as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For research involving prisoners, Minimal Risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

Please complete the sections below if the research involves more than minimal risk to subjects, otherwise indicate each section as not applicable.

9.1 Periodic evaluation of data

Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Rare risk of reaction to Lumason – if any reactions occur, it will be known at the time of the exam and will be recorded/reported in REDCap The PI will perform this study and will be aware of any reactions at that time. Additionally, this data will be reviewed monthly by the PI. Lumason will be administered per standard of care (FDA-approved), as used in the radiology department at Penn State Health. Contrast reactions will be managed per standard practice, as CT or MRI contrast reactions are handled.

9.2 Data that are reviewed

Describe the data that are reviewed, including safety data, untoward events, and efficacy data.

Patients are monitored for at least 15 minutes after injection of contrast, which is greater than how long the contrast bubbles remain intact in the circulation. Patients have a phone number on their consent form to call if there are any delayed concerns or reactions.

Monitoring and recording of any contrast reactions at the time of the ultrasound. Reported to the PI who will review monthly in aggregate to evaluate any trends. Standard of care TACE and follow-up CT/MRI will not be monitored for reactions.

9.3 Method of collection of safety information

Describe the method by which the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls and with subjects).

As part of the case report form – reactions will be known at the time of the exam. It will be reported on the form, and recorded in REDCap. The PI will review these monthly in aggregate to evaluate for any trends.

9.4 Frequency of data collection

Describe the frequency of data collection, including when safety data collection starts.

Adverse events will be recorded at each imaging time point.

9.5 Individuals reviewing the data

Identify the individuals who will review the data. The plan might include establishing a data and safety monitoring committee and a plan for reporting data monitoring committee findings to the IRB and the sponsor.

PI – Dr. McGillen.

9.6 Frequency of review of cumulative data

Describe the frequency or periodicity of review of cumulative data.

Monthly

9.7 Statistical tests

Describe the statistical tests for analyzing the safety data to determine whether harms are occurring.

Large scale studies have been reported in the use of Lumason, including in patients with chronic liver disease have very low rates of reaction (<1%) and very rare severe reactions. Data will be reviewed monthly and if any reactions occur in that timeframe, the set will be given to the statistician to determine if rates are the same or above reported rates.

9.8 Suspension of research

Describe any conditions that trigger an immediate suspension of research.

Higher reaction rates (allergic) than reported studies.

10.0 Risks

List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration and reversibility of the risks. Consider all types of risk including physical, psychological, social, legal, and economic risks. Note: Loss of confidentiality is a potential risk when conducting human subject research.

- If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

- If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.
- If applicable, describe risks to others who are not subjects.

Lumason Risk

- Serious Cardiopulmonary Reactions: Serious cardiopulmonary reactions, including fatalities have occurred uncommonly during or shortly following administration of ultrasound contrast agents, including Lumason. These reactions typically occurred within 30 minutes of administration. The risk for these reactions may be increased among patients with unstable cardiopulmonary conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias).
- Ventricular Arrhythmia Related to High Mechanical Index
- Hypersensitivity Reactions: There is a very small risk of allergic reaction to Lumason, the ultrasound contrast material
- Systemic Embolization: When administering Lumason to patients with cardiac shunt, microspheres can bypass filtering by the lung and enter the arterial circulation.
- Risks of Lumason injection: The discomfort associated with injecting Lumason is a slight pinch or pin prick when the sterile needle enters the skin. The risks include mild discomfort and/or a black and blue mark at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure.

Table 1. Adverse Reactions in Adult Patients* n = 6856	
Number (%) of Patients with Adverse Reactions	340 (5%)
Headache	65 (1%)
Nausea	37 (0.5%)
Dysgeusia	29 (0.4%)
Injection site pain	23 (0.3%)
Feeling Hot	18 (0.3%)
Chest discomfort	17 (0.2%)
Chest pain	12 (0.2%)
Dizziness	11 (0.2%)
Injection Site Warmth	11 (0

*occurring in at least 0.2% of patients

Other Risks

- Discomfort includes the extra time required to perform the CEUS and to fill out the survey (estimated 30-45 minutes). Subjects are free to skip any questions that they prefer not to answer.
- Loss of confidentiality.

11.0 Potential Benefits to Subjects and Others

11.1 Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research. If there is no direct benefit to subjects, indicate as such. Compensation is not considered a benefit. Compensation should be addressed in section 13.0.

There is no direct benefit to the patient at the time of their study.

11.2 Potential Benefits to Others

Include benefits to society or others.

If CEUS is shown to be non-inferior to CT/MRI, there would be several different benefits to future patients (and potentially the subject themselves, in follow-up) –

This study has the potential to specifically affect patients with cirrhosis or other liver diseases who have been diagnosed and treated for HCC, often used as a bridge to transplantation. Four phase CT and contrast enhanced MRI are the standard methods for establishing the success of TACE treatment by looking for residual disease and for new tumor, but may be contraindicated or not feasible in certain patients. CEUS has a safer overall risk profile and is also significantly less expensive than CT or MRI. Contrast reactions are rare in CEUS, the exam has less contraindications than CT or MRI. Additionally, multiple separate doses can be administered in CEUSto get a second or better look at an area of concern in the liver.

Intrinsically, ultrasound has high spatial resolution and has a potential for identifying residual or recurrent tumor at the same rates and potentially even earlier than a CT scan can, where ethiodol can obscure subtle signs of residual tumor (23). This would ensure that HCC patients are triaged appropriately and potentially decreases morbidity with a safe, accurate, and less expensive bridge to liver transplantation.

12.0 Sharing Results with Subjects

Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how information will be shared.

Results of the research ultrasound with Lumason will not be shared with subjects. CT/MRI results will be shared via standard of care via radiologist dictation available in the electronic medical record.

13.0 Subject Payment and/or Travel Reimbursements

Describe the amount, type (cash, check, gift card, other) and timing of any subject payment or travel reimbursement. If there is **no** subject payment or travel reimbursement, indicate as not applicable.

Extra or Course Credit: Describe the amount of credit **and** the available alternatives. Alternatives should be equal in time and effort to the amount of course or extra credit offered. It is not acceptable to indicate that the amount of credit is to be determined or at the discretion of the instructor of the course.

Approved Subject Pool: Indicate which approved subject pool will be used; include in response below that course credit will be given and alternatives will be offered as per the approved subject pool procedures.

Subjects will receive a gift card at the conclusion of the CEUS appointment – specifically, after the CEUS AND CT/MRI AND after they have completed the one time survey. Amount is $50 per subject and is administered one time, at that visit.

14.0 Economic Burden to Subjects

14.1 Costs

Describe any costs that subjects may be responsible for because of participation in the research.

The TACE, follow-up CT and MRI imaging are standard of care and will be billed per usual, standard of care. The CEUS and Lumason used for the exam as the research arm, will not be charged to the patient or their insurance. The patient will not assume any additional added costs due to participation.

14.2 Compensation for research-related injury

If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

If there is no sponsor agreement that addresses compensation for medical care for research subjects with a research-related injury, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

For sponsored research studies with a research agreement with the sponsor that addresses compensation for medical care for research-related injuries, include the following text as written - DO NOT ALTER OR DELETE:
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Such charges may be paid by the study sponsor as outlined in the research agreement and explained in the consent form.

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Resources Available

15.1 Facilities and locations

Identify and describe the facilities, sites and locations where recruitment and study procedures will be performed.

If research will be conducted outside the United States, describe site-specific regulations or customs affecting the research, and describe the process for obtaining local ethical review. Also, describe the principal investigator's experience conducting research at these locations and familiarity with local culture.

Subjects will be identified and enrolled during the clinician office visit, if seen by a sub investigator or at the time of TACE in the CVIR suite.

Their follow-up CT/MRI and CEUS will be performed at either the main hospital or the East Campus location on the Penn State Health Hershey main campus grounds, due to convenience and privacy of the patient – CT/MRI and Ultrasound will be completed at the same location (in adjacent rooms/same hallway). Patient will not be required to leave the area to have all of the tests done.

15.2 Feasibility of recruiting the required number of subjects

Indicate the number of potential subjects to which the study team has access. Indicate the percentage of those potential subjects needed for recruitment.

In the past year, 160 TACE procedures were performed in the Cardiovascular Interventional Suite at Hershey Medical Center, which provides an adequate recruitment pool to meet our enrollment goal.

15.3 PI Time devoted to conducting the research

Describe how the PI will ensure that a sufficient amount of time will be devoted to conducting and completing the research. Please consider outside responsibilities as well as other on-going research for which the PI is responsible.

Primary investigator will have sufficient time to devote to this research

15.4 Availability of medical or psychological resources

Describe the availability of medical or psychological resources that subjects might need as a result of their participation in the study, if applicable.

Not applicable

15.5 Process for informing Study Team

Describe the training plans to ensure members of the research team are informed about the protocol and their duties, if applicable.

Frequent meetings will occur between the PI and study team, as a group and on an individualized basis, monthly and on an as-needed basis.

16.0 Other Approvals

16.1 Other Approvals from External Entities

Describe any approvals that will be obtained prior to commencing the research (e.g., from engaged cooperating institutions IRBs who are also reviewing the research and other required review committees, community leaders, schools, research locations where research is to be conducted by the Penn State investigator, funding agencies, etc.).

Not applicable

16.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – **Penn State** Health **only** – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of "HRP-902 - Human Tissue For Research Form" in CATS IRB.

☐ Animal Care and Use – **All campuses** – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – **All campuses** – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – **Penn State Health only** – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes but are no longer needed for clinical use. Upload a copy of "HRP-901 - Human Body Fluids for Research Form" in CATS IRB.

☐ Clinical Research Center (CRC) Advisory Committee – **All campuses** – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – **All campuses** – Research has one or more of study team members indicated as having a financial interest.

☒ Radiation Safety – **Penn State Health only** – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of "HRP-903 - Radiation Review Form" in CATS IRB.

☐ IND/IDE Audit – **All campuses** – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – **Penn State Health only** – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Health Cancer Institute (PSCI) Protocol Review Committee or the PSCI Disease Team is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website.

17.0 Multi-Site Study

If this is a multi-site study (i.e., a study in which two or more institutions coordinate, with each institution completing all research activities outlined in a specific protocol) and the Penn State PI is the lead investigator, describe the processes to ensure communication among sites in the sections below.

17.1 Other sites

List the name and location of all other participating sites. Provide the name, qualifications and contact information for the principal investigator at each site and indicate which IRB will be reviewing the study at each site.

Not applicable

17.2 Communication Plans

Describe the plan for regular communication between the overall study director and the other sites to ensure that all sites have the most current version of the protocol, consent document, etc. Describe the process to ensure all modifications have been communicated to sites. Describe the process to ensure that all required approvals have been obtained at each site (including approval by the site's IRB of record). Describe the process for communication of problems with the research, interim results and closure of the study.

Not applicable

17.3 Data Submission and Security Plan

Describe the process and schedule for data submission and provide the data security plan for data collected from other sites. Describe the process to ensure all engaged participating sites will safeguard data as required by local information security policies.

Not applicable

17.4 Subject Enrollment

Describe the procedures for coordination of subject enrollment and randomization for the overall project.

Not applicable

17.5 Reporting of Adverse Events and New Information

Describe how adverse events and other information will be reported from the clinical sites to the overall study director. Provide the timeframe for this reporting.

Not applicable

17.6 Audit and Monitoring Plans

Describe the process to ensure all local site investigators conduct the study appropriately. Describe any on-site auditing and monitoring plans for the study.

Data and subject safety related to this trial will be discussed at regularly scheduled meetings between the PI and study team. These meetings will occur every six months from the time of the first subject enrolled and will continue at this interval for the duration of active subjects enrolled. The frequency of meeting may change depending upon enrollment. Items to be reviewed include but are not limited to number of subjects treated, significant toxicities observed, other reportable events. data entry, and overall enrollment. Meeting minutes will be taken and provided to the DSMC upon request at and at time of DSMC review.

18.0 Adverse Event Reporting

18.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.0 Study Monitoring, Auditing and Inspecting

19.1 Auditing and Inspecting

By submitting this study for review, you agree to the following statement – DO NOT ALTER OR DELETE:

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

20.0 Future Undetermined Research: Data and Specimen Banking

If this study is collecting **identifiable** data and/or specimens that will be banked for future **undetermined research**, please describe this process in the sections below. This information should not conflict with information provided in section 22 regarding whether or not data and/or specimens will be associated with identifiers (directly or indirectly). If **NOT applicable**, indicate as such below in all sections.

20.1 Data and/or specimens being stored

Identify what data and/or specimens will be stored and the data associated with each specimen.

All data collected for this study will be stored in REDCap and Oncore. Study team only as access – REDCap is a web-based database collection through Penn State; it is double password protected.

20.2 Location of storage

Identify the location where the data and/or specimens will be stored.

REDCap, Oncore, which are online, secure, password protected sites for data collection at Penn State.

20.3 Duration of storage

Identify how long the data and/or specimens will be stored. If data and/or specimens will be stored indefinitely, indicate as such.

Up to 5 years from study completion

20.4 Access to data and/or specimens

Identify who will have access to the data and/or specimens.

PI and sub PIs

20.5 Procedures to release data or specimens

Describe the procedures to release the data and/or specimens, including: the process to request a release, approvals required for release, who can obtain data and/or specimens, and the data to be provided with the specimens.

Not applicable, will not be released.

20.6 Process for returning results

Describe the process for returning results about the use of the data and/or specimens.

Not applicable

21.0 References

List relevant references in the literature which highlight methods, controversies, and study outcomes.

1. Zheng W, Li Q, Zou XB, et al. Evaluation of Contrast-enhanced US LI-RADS version 2017: Application on 2020 Liver Nodules in Patients with Hepatitis B Infection. *Radiology*. 2019: Epublished ahead of print.
2. Watanabe Y, Ogawa M, Kumagawa M, et al. Utility of contrast-enhanced ultrasound for early therapeutic evaluation of hepatocellular carcinoma after transcatheter arterial chemoembolization. *J Ultrasound Med.* 2019; Epublished ahead of print.
3. Moschouris H, Kalokairinou-Motogna M, Vrakas S, et al. Imaging of intrahepatic progression of hepatocellular carcinoma post transarterial chemoembolization. A long-term, prospective evaluation of contrast enhanced ultrasound. Med Ultrason. 2017;19(2):134-42.
4. Paul SB, Dhamija E, Gamanagatti SR, et al. Evaluation of tumor response to intra-arterial chemoembolization of hepatocellular carcinoma: Comparison of contrast-enhanced ultrasound with multiphase computed tomography. *Diagn Interv Imaging.* 2017;98:253-260.
5. Cho YZ, Park SY, Choi EH, et al. The usefulness of contrast-enhanced ultrasonography in the early detection of hepatocellular carcinoma viability after transarterial chemoembolization: Pilot study. *Clin Mol Hepatol*. 2015;21(2):165-174.
6. Huang K, Kiu YJ, Wang XM, Jiang B, Zhai QX, Bian DL. Control study of contrast enhanced ultrasound and contrast enhanced CT in the curative effect of hepatoceullar carcinoma after TACE. *Mod Oncol*. 2015;23:2670-2673.
7. Liu M, Lin MX, Lu MD, et al. Comparison of contrast-enhanced ultrasound and contrast-enhanced computed tomography in evaluating the treatment response to transcatheter arterial chemoembolization of hepatocellular carcinoma using modified RECIST. *Eur Radiol*. 2015;25:2502-2511.
8. Xu Y, Cao CW, Lu CH, Li YC, Li MQ, Yang JH. The role of ultrasonography in the evaluation of early-micro-perfusion after chemoembolization of hepatocellular carcinoma. *Chin J Interv Radiol.* 2014;2:52-55.
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22.0 Confidentiality, Privacy and Data Management

IMPORTANT: The following section is required for all locations EXCEPT Penn State Health and the College of Medicine. Penn State Health and College of Medicine should skip this section and complete "HRP-598 Research Data Plan Review Form." In order to avoid redundancy, for this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all other sub-sections of section 22.

<u>For research being conducted at Penn State Health or by Penn State Health researchers only</u>: The research data security and integrity plan is submitted using "HRP-598 – Research Data Plan Review Form."

Refer to Penn State College of Medicine IRB's "Standard Operating Procedure Addendum: Security and Integrity of Human Research Data," which is available on the IRB's website. In order to avoid redundancy, for

this section state "See the Research Data Plan Review Form" if you are conducting Penn State Health research. Delete all sub-sections of section 22.

For all other research: complete the following section. Please refer to PSU Policy AD95 for information regarding information classification and security standards and requirements. It is recommended that you work with local IT staff when planning to store, process, or access data electronically to ensure that your plan can be carried out locally and meets applicable requirements. If you have questions about Penn State's Policy AD95 or standards or need a consultation regarding data security, please contact security@psu.edu.

See the Research Data Plan Review Form