Version Date: November 3, 2021

CONSENT FOR RESEARCH
Penn State College of Medicine
Penn State Health

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

Principal Investigator: Dr. Kathryn McGillen

Address: 500 University Drive, Hershey, PA 17033

Telephone Numbers: Weekdays: 8:00 a.m. to 5:00 p.m. (717) 531-6284. After hours call (717) 531-8521. Ask for the Radiology doctor on 24-hour call.

Subject's Printed Name: _____

We are asking you to be in a research study.

Whether or not you take part is up to you. You can choose not to take part. You can agree to take part and later change your mind. Your decision will not be held against you, and there will be no penalty or loss of benefits to which you are entitled.

This form gives you information about the research. Please ask questions about anything that is unclear to you and take your time to make your choice.

KEY INFORMATION

The following is a short summary of this study to help you decide whether or not to be a part of this research. More detailed information is provided later in this form. If you have any questions, be sure to ask the study team.

Why am I being invited to take part in this research study?
We are asking you to take part in this voluntary research study because you are planning to have a standard-of-care transarterial chemoembolization (TACE) procedure. TACE is a specific type of chemoembolization that blocks a blood vessel as a way to treat your liver hepatocellular carcinoma (HCC), a type of liver cancer.

What is the purpose of this research study?
The purpose of this voluntary research study is to find out if a different type of imaging study called contrast enhanced ultrasound (CEUS) is as good as, or better than CT or MRI in patients diagnosed with hepatocellular carcinoma (HCC) after receiving TACE treatment.

How long will the research study last?
If you agree to take part, it will take you about 4 months to complete this research study. You will only be asked to complete additional research related procedures at your first follow-up imaging visit, after your TACE treatment.

What will I need to do?
We will use information from your medical records and information collected during your TACE consent to determine if you are eligible for this research study. If you are eligible, you will return to Penn State Health after your first TACE treatment for your follow-up standard-of-care MRI or CT scan. The timing of this follow-up will be followed as routinely ordered by your providers. You and your doctor will decide if you are to have an MRI or a CT scan.

At this visit you will also have a research related contrast enhanced ultrasound (CEUS). An ultrasound procedure is performed to look for the known, treated lesion and any other new lesions.

You will be asked to answer a short survey about your preferences and experience after both the standard-of-care and research scans have been completed.

Lastly, as part of standard clinical care, you will be scheduled for further follow-up imaging (either a CT or an MRI). You will not be asked to do any additional research tasks at that visit, but the research team will review and include information from your that imaging in the research study.

What are the main risks of taking part in the study?
For this study, the main risks to know about are:

- Serious heart and lung reactions, including fatalities have occurred uncommonly during or shortly following administration of ultrasound contrast agents, including Lumason.
- Abnormal heartbeats in the lower heart chambers (ventricles)
- There is a very small risk of allergic reaction to Lumason, the ultrasound contrast material
- When administering Lumason to patients with cardiac shunts, small particles can enter and cause a blockage in the main artery.
- 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.

What are the possible benefits to me that may reasonably be expected from being in the research?
There are no benefits to you from taking part in this research. Results of the study may benefit other people in the future by helping us learn more about treatment for HCC.

What happens if I do not want to be in this research?
Participation in research is completely voluntary. You can decide to participate or not to participate.

DETAILED INFORMATION
The following is more detailed information about this study in addition to the information listed above.

1. Why is this research study being done?
You are being asked to volunteer for this research study because you are planning to have a standard-of-care transarterial chemoembolization (TACE) procedure. TACE is a specific type of chemoembolization that blocks a blood vessel as a way to treat your liver hepatocellular carcinoma (HCC), a type of liver cancer. Patients at Penn State Health typically have a computed tomography (CT or CAT) scan or magnetic resonance imaging (MRI Scan) scan 2 to 4 months after TACE. Doctors use these imaging studies to see how much the tumors have shrunk and to look for any new tumors in the liver. This research is being done to find out if different type of imaging study called contrast enhanced ultrasound

(CEUS) is as good as, or better than CT or MRI in patients diagnosed with hepatocellular carcinoma (HCC) after receiving TACE treatment.

CEUS is a medical test that uses high-frequency sound waves to capture live images from the inside of your body. The use of a contrast agent improves a doctor's ability to find liver tumors using ultrasound. The contrast agent called Lumason ® being used for this research contains gas-filled micro-bubbles that are injected into a blood vessel in your arm. Lumason ® is approved by the United States Food and Drug Administration (FDA) for ultrasound imaging in adults to find liver lesions (tumors) and it is commercially available in the United States and other countries.

Approximately 34 people will take part in this research study at Penn State Health.

2. What will happen in this research study?

If you agree to participate in this research, you will first review and sign this consent form before any research-related activities occur. After you consent, we will use information from your medical records and information collected during your TACE consent to determine if you are eligible for this research study.

Timepoint 0

You will complete your first standard of care TACE treatment. After this, you will be scheduled for follow-up imaging according to your treating physician's recommendation.

Timepoint 1

All research study participants will have both the standard of care CT or MRI and a one-time research related contrast enhanced ultrasound (CEUS) at the same appointment. For your standard of care imaging, you and your doctor will decide if you are to have an MRI or a CT scan.

Your standard of care imaging (CT or MRI) and the research related imaging (CEUS) will occur in adjacent rooms at the same visit.

An ultrasound procedure is performed to look for the known, treated lesion and any other new lesions. If a lesion(s) is visible, you will have an IV placed, if not already in place from your CT/MRI. The same IV will be used for the ultrasound and CT/MRI. If no lesion is visible, the IV from CT/MRI will be removed, if it was already in place. A radiologist will inject the contrast. 2.4 mL of Lumason is injected via the IV, followed by a sterile saline flush (5-10 mL). More than one dose of the contrast will be used if deemed necessary (such as suboptimal positioning of the first dose, or to evaluate a second lesions), which is standard of care. The radiologist will then perform ultrasound imaging of the liver for up to 5 or 6 minutes. Once the ultrasound and CT/MRI are complete, your IV will be removed.

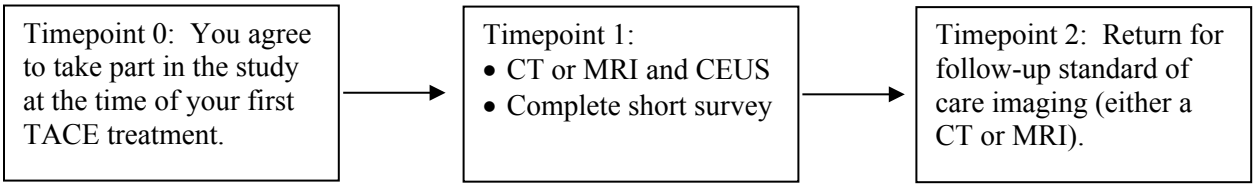
You will be asked to answer a short survey about your preferences and experience after both the standard-of-care and research scans have been completed. You are free to skip any questions that you prefer not to answer.

Your doctor will contact you about standard of care CT or MRI test results. However, you will not be informed of the test results for the research CEUS. These results will be examined for research purposes only. The research related procedures at this visit (CEUS and survey) will take an additional 30-45 minutes.

Timepoint 2

Lastly, as part of standard clinical care, you will be scheduled for further follow-up imaging (either a CT or an MR). This visit will be scheduled as per standard of care. You will not be asked to do any additional research tasks at that visit, but the research team will review and include information from your imaging in the research study.

Another way to find out what your experience will be during this research study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



3. What are the risks and possible discomforts from being in this research study?

Lumason Risk

- Serious Heart and Lung Reactions: Serious heart and lung 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 heart and/or lung conditions (acute myocardial infarction, acute coronary artery syndromes, worsening or unstable congestive heart failure, or serious ventricular arrhythmias).
- Abnormal heartbeats in the lower heart chambers (ventricles)
- There is a very small risk of allergic reaction to Lumason, the ultrasound contrast material
- When administering Lumason to patients with cardiac shunts, small particles can enter and cause a blockage in the main artery.
- 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%)
Altered or Impaired Sense of Taste	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. Precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained as required by applicable law and to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

4. What are the possible benefits from being in this research study?

4a. What are the possible benefits to me?

You will not benefit from this research study at this time.

4b. What are the possible benefits to others?

The results of this research may guide the future treatment of HCC.

5. What other options are available instead of being in this research study?

You do not have to take part in this study to be treated for your condition. Instead of participating in this research, you could:

- Receive commercially available imaging, including ultrasound with Lumason ®.
- Be part of a different research study, if one is available.
- Choose not to be treated for your medical condition.
- Choose to have routine follow-up –CEUS, standard CT or MRI and not participate in a trial.

Before you decide if you want to be in this research, we will discuss the other choices that are available to you. We will tell you about the possible benefits and risks of these choices.

The therapy offered in this research is available to you without taking part in this research study

6. How long will I take part in this research study?

If you agree to take part, it will take you about 4months to complete this research study. You will only be asked to complete additional research related procedures at your first follow-up imaging visit, after your TACE treatment. The other visits do not require any time on your part.

7. How will you protect my privacy and confidentiality if I decide to take part in this research study?

7a. What happens to the information collected for the research?

Efforts will be made to limit the use and sharing of your personal research information to people who have a need to review this information. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed, and there may be situations where disclosure is required by law.

In our research files at Penn State Health (PSH) and Penn State College of Medicine (PSU) we will include these identifiers: name, address, date of birth, visit dates, medical record number, accession number (the number assigned to your images), and a code number. Your mobile phone number and/or email address will recorded, if you chose to provide them.

- A list that matches your name with your code number will be kept in a locked file in Dr. McGillen's office.
- Your research records will be labeled with your code number and will be kept in a safe area in Dr. McGillen's research office.
- A copy of this signed consent form will be included in your PSH medical record. This means that other PSH healthcare providers will know you are in this study.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

7b. What will happen to my research information and/or samples after the study is completed?
We may use your research information in future studies or may share your information with other investigators for future research without your additional informed consent. Before we use or share your information we will remove any information that shows your identity.

7c. How will my identifiable health information be used?
In general, under federal law (including the Health Insurance Portability and Accountability Act – HIPAA or privacy laws) your health information is private. By signing this form, you are authorizing us to collect, use, and disclose your identifiable health information, sometimes referred to as "Protected Health Information" or "PHI" under HIPAA, for the purposes of this research study. We will use and disclose your information only as described in this form, in the PSH Privacy Notice, and as may be required or allowed under the applicable privacy laws.

The research team may use the following health information:

- Past, present, and future medical records, including identifiable information
- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

The following people/groups may see, use, and share your identifiable health information:

- PSH/PSU research staff involved in this study
- The PSH/PSU Institutional Review Board (IRB), a group of people who review the research study to protect subjects' rights and welfare
- The PSH/PSU Human Subjects Protection Office
- The PSH/PSU Research Quality Assurance Office
- Non-research staff within PSH/PSU who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- Federal and state agencies (such as the U.S. Food and Drug Administration, the Office for Human Research Protections, the Department of Health and Human Services, the National

Institutes of Health, and other U.S. or foreign government bodies that oversee or review research)
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Organizations that provide independent accreditation and oversight of hospitals and research
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)

These groups may also review and/or copy your original PSH/PSU records while looking at the results of the research study. It is possible that some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information. We share your information only when we must, and we ask anyone who receives it from us to protect your privacy.

Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your identifiable health information and samples may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

We may remove identifying information from your protected health information. Once we do this, the remaining information will not be subject to the privacy laws. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Because research is an ongoing process, your permission for the use, storage and sharing of your health information will continue indefinitely.

Your privacy rights:
- You have the right to refuse to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you will not be able to take part in this research study.
- You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing using the address on the front of this form. Once permission is withdrawn, you cannot continue to take part in the study.
- If you withdraw your permission, we will stop collecting health information about you for this study; we may continue to use and share your health information that we already have if it is necessary for safety and scientific soundness of the research study; and we will not be able to take back information that has already been used or shared with others.
- You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. However, you may not be allowed to see or copy certain health information that is a part of this research study. This is only for the period of the study. You will be allowed to see that information when the entire research study is complete.

8. What are the costs of taking part in this research study?

8a. What will I have to pay for if I take part in this research study?

For costs of tests and procedures that are <u>only</u> being done for the research study:
- The contrast enhanced ultrasound (CEUS) will be provided at no cost to you while you take part in this study.

- You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research and are outside the standard of care (what is normally done) for your condition.
- The research-related tests and procedures that will be provided at no cost to you include: CEUS and the contrast Lumason.

For costs of medical services for care you would receive even if you were not in this research study:

- You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research.
- You and/or your insurance company will be billed for the costs of these routine tests and procedures in the usual manner.
- You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage.
- You will be responsible for any charges not reimbursed by your insurance company.
- Some insurance companies may not pay for routine costs for people taking part in research studies. Before deciding to be in this research you should check with your insurance company to find out what they will pay for.

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team.

8b. What happens if I am injured as a result of taking part in this research study?
It is possible that you could develop complications or injuries as a result of being in this research study. If you experience a side effect or injury and emergency medical treatment is required, seek treatment immediately at any medical facility. If you experience a side effect or injury and you believe that emergency treatment is not necessary, you should contact the principal investigator listed on the first page of this consent form as soon as possible and the principal investigator will arrange for medical treatment. You should also let any health care provider who treats you know that you are in a research study.

<u>PSH/PSU compensation for injury</u>

- There are no plans for PSH/PSU to provide financial compensation or free medical treatment for research-related injury.
- If an injury occurs, medical treatment is available at the usual charge.
- Costs will be charged to your insurance carrier or to you.
- Some insurance companies may not cover costs associated with research injuries.
- If these costs are not covered by your insurance, they will be your responsibility.

When you sign this form you are not giving up any legal right to seek compensation for injury.

9. Will I be paid to take part in this research study?
You will receive $50.00 for completing the CEUS and the survey. The payment will be provided by Greenphire Clincard.

This reimbursement will be issued by an external company called Greenphire, which will issue your reimbursement. You will be issued a ClinCard, which is a debit card that your funds are loaded onto and can be used at your discretion. The research team will give Greenphire some personal information about you, as described below. Greenphire will only use your personal information to process this

reimbursement and will not share it with anyone for any other purpose. Details of the debit card system are explained on an additional sheet. If you lose the card, you may be responsible for the replacement fee.

When a visit is completed, funds will be approved and loaded onto your card. The funds will be available within 2-3 business days. In order to assign a ClinCard to you and load funds onto the ClinCard, Greenphire will need your Study/Subject ID, Name, Address, date of birth, and Social Security Number.

You will have the option to receive updates related to payment alerts via text message and/or email message. Standard text messaging rates will apply. In order to send you messages Greenphire will need your Mobile Phone Number and/or E-mail Address.

Payment received as compensation for participation in research is considered taxable income. If payments from Greenphire exceed $600 in any one calendar year, Greenphire will file a 1099 (Miscellaneous Income) form on behalf of Penn State.

10. Who is paying for this research study?
The institution and investigators are receiving a grant from Hershey Medical Center-Liver Center Research Fund Pilot Award to support this research.

11. What are my rights if I take part in this research study?
Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect medical information from your routine medical care. If you withdraw completely from the research study, no further information will be collected and your participation will end. You may discontinue taking part at any time without penalty or loss of benefits to which you are otherwise entitled.

Your research doctor may take you out of the research study without your permission.

- Some possible reasons for this are: you become pregnant, develop an allergic reaction to Lumason, continuing the research would be harmful, you experience a serious side effect, or if you do not return for CEUS after your TACE treatment.
- Also, the sponsor of the research may end the research study early.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

12. If I have questions or concerns about this research study, whom should I call?
Please call the head of the research study (principal investigator), Dr. McGillen at (717) 531-6284, the co-Investigator, Dr. Waybill at (717) 531-5418, or the Radiology doctor on 24-hour call at (717) 531-8521.

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

You may also contact the research protection advocate in the PSH Human Subjects Protection Office (HSPO) at (717) 531-5687 if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns, complaints or general questions about the research.
- Have questions about your privacy and the use of your personal health information.
- You may also call this number if you cannot reach the research team or wish to offer input or to talk to someone else about any concerns related to the research.

You may visit the Penn State College of Medicine's Clinical Research web site at http://med.psu.edu/clinical-research/faqs for:

- Information about your rights when you are in a research study;
- Information about the Institutional Review Board (IRB), a group of people who review the research to protect your rights; and
- Links to the federal regulations and information about the protection of people who are in research studies. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (717) 531-5687.

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

Version Date: November 3, 2021

INFORMED CONSENT AND AUTHORIZATION TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative, provided the subject or subject representative an opportunity to discuss and consider whether or not to participate in the research, and have answered any questions about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent and Authorization

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject

By signing this consent form, you indicate that you voluntarily choose to be in this research and authorize your information to be used and shared as described above.

_____	_____	_____	_____
Signature of Subject	Date	Time	Printed Name