Department of Veterans Affairs

RESEARCH CONSENT FORM

Title of Study: Noninvasive Assessment of Treatment-induced Hypoxia in Patients with Hepatocellular Carcinoma Undergoing Transcatheter Arterial Embolization: a Feasibility Study with 18F-FMISO PET/CT	
Title of Consent (if different from Study Title):	
Principal Investigator: **Rajesh Shah, MD**	VAMC: VA Palo Alto HCS

Are you participating in any other research studies? _____ yes _____no

PURPOSE OF RESEARCH

You are invited to participate in a research study of the treatment of hepatocellular carcinoma, a type of liver cancer. Through the use of a new imaging study, we hope to learn whether changes occur in the tumors after treatment, which can then help us decide how well the treatment worked earlier than is currently possible. You were selected as a possible subject in this study because you have liver cancer and may require a treatment, called embolization, for the tumors in the liver.

This study is being done together by researchers at VA Palo Alto and Stanford University.

This research study is looking for 5 people with liver cancer requiring treatment of the cancer. The VA Palo Alto expects to enroll 5 research study subjects.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care you are entitled to.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 1 year to complete. 6 months of your participation will be required. Two days of your active participation will be required for the imaging study being researched. The remaining time will be treatments, tests, and follow-up visits that will be obtained whether or not you participate in the study.

PROCEDURES

If you choose to participate, the investigators will schedule you for all visits and procedures. If you do not have a CT scan or MRI of your liver within the previous month, you will be scheduled for a repeat scan to determine if there are any changes to your liver tumors. “Tumor” is another word for your liver cancer. This

scan will be done regardless of whether you participate in the study or not. Once this is completed, your CT or MRI scan, blood tests, and medical history will be used to determine if you are eligible for the study. If you are eligible, you will be scheduled for a special scan, called an FMISO PET/CT scan. This scan requires being given an injection of a radiopharmaceutical (a special medication with low levels of radiation that lasts less than one day) called ^{18}F-FMISO, then having images taken for approximately 2 hours after the injection. For the imaging, you will need to lay flat on a table for about 1-2 hours. This scan is part of the research study and would not be performed if you do not enroll in the study.

Within 4 weeks of the FMISO PET/CT scan you will undergo embolization of your liver tumors. This procedure will be performed whether or not you participate in the study. For this procedure, you will have a catheter (a long, narrow tube), placed into the large blood vessel of your leg (called an artery), which will then be used to find the arteries of the liver feeding the tumors. Once these arteries are identified using contrast (or "dye") injection and x-rays, the arteries will be blocked up using very small particles. These particles are semi-permanent and prevent blood from reaching the tumors. The tumors rely on this blood supply to survive. Without the blood supply, the tumors cannot survive. Once the arteries are blocked up, the catheter is removed and a small plug is placed on the artery to close it. Only a small bandage is left on the skin. No large incisions or sutures are used. You will be admitted to the hospital overnight after this procedure for observation and to help with any nausea, vomiting, and pain that you might experience. This will also be done whether or not you participate in the study.

The day after the embolization procedure, while you are still in the hospital, you will undergo a second FMISO PET/CT scan. This scan will be performed in the same way as the previous scan, described above. This scan is also part of the research study and would not typically be performed. After the scan is completed, if you are feeling well, you will be discharged from the hospital. If you are still having symptoms related to the embolization procedure, you will be kept in the hospital until you have recovered adequately.

Approximately 2 months after the procedure, you will undergo a repeat CT or MRI scan to determine how the tumors have responded. This scan will be done whether or not you participate in the study. If there are any residual tumors, you can continue to undergo any treatment that would normally be done.

Approximately 3 months later, you will undergo a repeat CT or MRI scan. Again, this scan will be done whether or not you participate in the study. If there are any residual tumors, you can continue to undergo any treatment that would normally be done. After this final scan, your participation in the study will be complete. You will continue to undergo your usual follow-up and treatment for your liver cancer without any restrictions.

In summary, the tests in this study that are purely for research are the ^{18}F-FMISO PET/CT scans, of which 2 will be performed. These are not typically performed as part of your treatment for liver cancer.

The CT or MRI scans and embolization treatments along with any follow-up clinic visits and labs will be performed whether or not you participate in the study.

MRI (Magnetic Resonance Imaging)

MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for a certain amount of time, about 1-2 hours, while the machine gathers data. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance (MR) scanner. We will provide earplugs or headphones that you will be required to wear. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

Risks:

Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye

injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator.

If you have had a previous reaction to Gadolinium-based contrast agents or a history of severe allergies, please notify the operator/investigator. If you have kidney problems, please tell the operator.

Dizziness or nausea may occur if you move your head rapidly within the magnet.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

Women of Childbearing Potential

If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study. You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the investigators and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the investigators or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the investigators or research study staff about any side effects, doctor visits, or hospitalizations that you may have.

- Tell the investigators or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Ask questions as you think of them.
- Tell the investigators or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are **free to withdraw** your consent and stop your participation at any time. If you decide to withdraw from the study, you will not lose any benefits to which you would otherwise be entitled and your decision will not affect your ability to receive medical care for your condition.

If you want to stop being in the study you should tell the investigators or study staff. You can do this by phone by calling Dr. Rajesh Shah at [redacted] extension [redacted]

If you withdraw from the study,

- You will not be able to undergo the ^{18}F-FMISO PET/CT scan
- You will continue to undergo standard-of-care treatments for you liver tumors which include embolization, chemotherapy, ablative therapies, and possibly surgery
- You will continue to undergo CT or MRI scans to follow your liver tumors in order to determine if any treatments are needed

The investigators may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions of the investigators and/or study staff.
- The investigators decide that continuing your participation could be harmful to you.
- Pregnancy (if applicable).
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

Participation in this study may involve risks to you. In prior studies these risks have been shown to be:

- ^{18}F-FMISO PET/CT Scan: The doses administered are extremely small, and there is no known risk of the FMISO at these levels. However, there is a theoretical risk of allergic reaction to any medication. There is the risk of increased radiation exposure if you agree to participate. This research study involves exposure to radiation from two FMISO PET/CT studies. This radiation exposure is not necessary for your medical care and is for research purposes only. The additional amount of radiation exposure is about 16.8 mSv, which is approximately equal to 34% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year. This amount of radiation involves minimal risk and is necessary to obtain the research information desired. Because of the limited experience in humans of this radioisotope, there is the possibility of risks that are currently unforeseeable.

- Transcatheter arterial embolization: There are risks involved with the mesenteric angiography and the embolization during this procedure. A mesenteric angiogram is a procedure in which a catheter (long narrow tube) is guided from a blood vessel in the leg (common femoral artery) into the blood vessel of the liver (hepatic artery) and is an essential part of procedure. Potential side effects and complications include groin soreness and bruise formation (less than 4%), damage to the blood vessels as a result of wire and catheter manipulation that results in failure to treat the liver (less than 1%), formation of a blood clot resulting in blockage of a blood vessel (less than 1%), infection (less than 1%). Risks from the embolization procedure include side effects resulting from particles lodging into areas outside the liver (called non targeted embolization). Although this is rare (less than 2%), blockage of the blood vessels relating to the lungs, stomach, pancreas, gall bladder, and digestive tract may result in ulceration or inflammation. Reports of particles lodging into the lung resulting in death are extremely rare. In addition, embolization has the possible risk of placing the liver into failure. Liver failure will usually not resolve and can lead to death. This potential complication is rare (less than 1%). You will likely have pain after the procedure in the abdomen near the liver. This usually resolves within 1 week and is well controlled with pain medication, which will be provided if needed. However, pain can last up to one month, or in rare instances, longer.
- You may experience some brief and /or minor discomfort associated with the tests required. For example, you may experience pain or bruising associated with the needle from an IV insertion or blood drawing. Fainting and local infection can also occur when blood is drawn, although this is rare. You may have discomfort related to the procedures including discomfort in having to lay flat for several hours during and after the procedures. There may be several inconveniences for participating in the study. The first is the inconvenience of travelling for the initial PET/CT scan, and that the second PET/CT scan may keep you in the hospital 3 hours longer than you otherwise would be observed.

POTENTIAL BENEFITS

There is unlikely to be any direct personal benefit for participating in this study.

However, there is a possibility that the information obtained in this study may help in the future development or improvement of treatment for patients who suffer from your condition.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY.

ALTERNATIVES

Your study doctor will discuss the risks and benefits of other treatments for your disease with you before you decide whether or not you want to participate in this study. You do not have to participate in this study to receive treatment for your cancer. If you decide not to participate in this study, your decision will not affect your medical care in any way. If you decide not to participate, you will not undergo any ^{18}F-FMISO PET/CT scans.

Your condition may already have been discussed and decided at a multidisciplinary tumor board involving several experts in the fields of surgery, radiology, hepatology, medical oncology and interventional radiology. Therefore, it is important that you discuss the benefits and risks of all treatment options with your doctor before signing this consent. If you choose to participate in the study, your study doctor will let you know if any new treatment for your condition becomes available which may affect your willingness to continue participation in this study.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

ClinicalTrials.gov

A description of this clinical trial will be available on http://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.

CONFIDENTIALITY

We will keep your name and all the information about you used in this study as confidential as possible. We may publish the results of this study for others to read about, but you will not be identified in any articles about the study by name, social security number, address, telephone number, or any other direct personal identifier. Also, other federal agencies as required, such as the VA Office of Research Oversight and the VA Office of the Inspector General may have access to your information.

Because this study involves an investigational drug, the Food and Drug Administration may also have access to information about you collected in this study.

FINANCIAL CONSIDERATIONS

Payment

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

Costs

There will be no costs to you for any of the treatment or testing done as part of this research study. However, medical care and services provided by the VA that are not part of this study (e.g., normal hospital and prescription expenses which are not part of the research study) may require co-payments if your VA-eligibility category requires co-payment for VA services.

Sponsor

Stanford University is providing financial support and/or material for this study.

COMPENSATION for Research Related Injury

If you are injured as a direct result of being in this study, medical treatment will be available. If you are eligible for veteran's benefits, the cost of such treatments will be covered by the VA. If not, the cost of such treatments may still be covered

by the VA depending on a number of factors. In most circumstances, the treatment must be provided in a VA medical facility. No other form of compensation for injuries is available. However, by signing this form you have not released the VA from liability for negligence. For further information, you may call the Human Protections Administrator at ([redacted] or the V.A. Regional Counsel at ([redacted]

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the principal investigator Dr. Rajesh Shah at [redacted].

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the principal investigator, principal investigator Dr. Rajesh Shah at [redacted].

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at ([redacted] or toll free at 1 [redacted]. You can also write to the Stanford IRB, Stanford University, [redacted]

Appointment Contact: If you need to change your appointment, please contact Interventional Radiology at [redacted].

Alternate Contact: If you cannot reach the principal investigator, please contact Interventional Radiology at [redacted]

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;

- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

Signing your name means you agree to be in this study and that you were given a copy of this consent form.

_____ _____

Signature of Participant Date

_____

Print Name of Participant

Department of Veterans Affairs

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Title of Consent (if different from Study Title):	
Principal Investigator: **Rajesh Shah, MD**	VAMC: VA Palo Alto HCS

_____ _____

Signature of Person Obtaining Consent Date

_____

Print Name of Person Obtaining Consent

HIPAA regulations require the participant to give separate written permission (signature) for the use of their protected health information.

Person Obtaining Consent HIPAA Authorization confirmation:

☐ Confirm the participant signed the VA HIPAA Authorization (VA 10-0493)