Focused Ultrasound and Pembrolizumab in Metastatic Breast Cancer

NCT03237572

Informed consent form – UVA IRB-HSR #19900 approved 07-15-2022

Consent of an Adult to Be in a Research Study

In this form "you" means a person 18 years of age or older who is being asked to volunteer to participate in this study.

Participant's Name_____ Medical Record # _____

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Funding Source:	Merck Sharp & Dohme Corporation UVA Focus Ultrasound Center
Supplier of Pembrolizumab:	Merck Sharp & Dohme Corporation
Manufacturer of Echopulse®:	Theraclion SA

What is the purpose of this form?

This form will provide you with information about this research study. You do not have to be in the study if you do not want to. You should have all your questions answered before you agree to be in this study.

Please read this form carefully. If you want to be in the study, you will need to sign this form. You will be given a signed copy of this form.

Who is funding this study?

The University of Virginia Human Immune Therapy Center is managing this study. Merck Sharp & Dohme Corporation is providing the pembrolizumab study drug and will also be providing some funding for this study. The UVA Focus Ultrasound Center will also be providing funding for this study. Theraclion SA, the company that makes the Echopulse device, is providing their device for use in this study.

Why is this research being done?

The purpose of this study is examine the effectiveness and safety of the combination of an investigational device called the Echopulse® with an investigational agent called pembrolizumab for the treatment of breast cancer.

Pembrolizumab is a type of antibody. Antibodies are part of your immune system and may be used to fight off bacteria, viruses, and cancer cells either directly or indirectly. Pembrolizumab is a special kind of antibody that is made in the laboratory. It binds to a protein which is found on immune cells. When this antibody binds to immune cells, it may help the immune cells to fight off cancer cells.

Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but is not approved by the Food and Drug Administration (FDA) for the treatment of breast cancer, and is considered investigational for the purpose of this study.

The Echopulse device is a computer driven system which uses ultrasound to guide a high intensity focused ultrasound beam to a targeted area (a tumor in the breast). The high intensity focused ultrasound (HIFU) heats the targeted site which causes the cells to die. **The Echopulse device is investigational, and has not been approved by the U.S. Food and Drug Administration (FDA).** So far, the device has been used in more than 600 people for treatment of a variety of clinical conditions including breast fibroadenomas, benign thyroid nodules and benign parathyroid nodules, both in commercial and experimental environment.

In this study, the investigational study drug pembrolizumab will be given in combination with the investigational Echopulse device HIFU treatment to target breast cancer.

You are being asked to be in this study, because you have metastatic or unresectable breast cancer and have had at least one prior line of therapy for breast cancer in the metastatic setting.
Up to 30 people may sign a consent form to participate in this study, and up to 15 may receive study treatment.

How long will this study take?

Your participation in this study will require up to 7 study visits over the first 3 months. If you continue study treatment, you may have additional study visits every 3 weeks for up to 2 years. The exact length of time that you participate in this study will depend on your response to study treatment. If you discontinue study treatment and meet certain criteria, you may be eligible for up to one year of additional study treatment. Each visit will last between 2 and 5 hours.

What will happen if you are in the study?

NOTE: Throughout the study, results of tests and procedures completed as part of your standard clinical care will also be recorded for research purposes. Some tests may be performed more frequently as part of the research study.

This study may be introduced to you by one of the members of your clinical team, or another member of the University of Virginia, such as a member of this study's research team. Before you agree to participate in this study, you will have an opportunity to review this consent form and to have all of your questions answered.

SCREENING (about 2-5 hours to complete and the procedures may be completed over multiple days):

Visit 1:

If you agree to participate, you will sign this consent form before any study related procedures take place. Before you can start in the study, there will be a screening period. You will have tests and procedures during this time to make sure you are eligible and it is safe for you to participate.

Further, the study team will want to have access to tests and procedures done prior to this study. The research team may ask you some questions and/or review your records for information and results, and may request copies of documents, which will become part of your study records.

- Information about you, such as your age, gender, race, and medical history will be collected.
- Your tumor specimen(s) may be reviewed by pathologists at UVA. This will be completed to evaluate or to confirm if you are eligible for this study.

The following procedures will be performed for **research purposes**:

- You will have a physical exam, which may include the following tests and procedures:
    - Vital signs (blood pressure, heart rate, temperature)
    - Height
    - Weight
    - Determine your ability to function and perform daily activities
    - Determine where on your body the HIFU treatment will be given
    - Record the medications that you are taking; including any over-the-counter, alternative medications, herbal medications, or supplements.

- About 1 to 2 tablespoons of blood will be drawn from a vein in your arm for the following tests:
    - For women, if you can get pregnant and have not had a pregnancy test performed within the past two weeks a blood pregnancy test will be completed. The safety of the study drug to the maturing fetus has not been evaluated; therefore, this test must be negative in order for you to participate in this study.
    - Check your blood counts, certain levels of fats, salts, and sugars, kidney and liver function, and your immune cell counts.
    - Check your LDH (lactic acid dehydrogenase). LDH is an enzyme in the body that helps detect tissue or cell breakdown and also can indicate the presence of cancer, meningitis (inflammation of the thin layers of tissue that cover and protect the brain and spinal cord) and other disorders.
    - Check how your blood clots.
    - About ½ tablespoon of blood will be drawn to test for HIV and Hepatitis B and Hepatitis C virus, if you have not had these tests completed within the past 6 months. Patients with HIV, and active Hepatitis B and Hepatitis C are not believed to be as likely to benefit from study treatment for their cancer, and/or may be best advised to seek treatment for those viral illnesses. Test results must be negative in order to participate in this study.

- You will have ultrasound imaging of the tumor in your breast intended for the HIFU treatment. Ultrasound imaging uses sound waves to image the tumor. This is being done to confirm that the Echopulse HIFU ultrasound beam would be able to reach the tumor.

- Scans will be performed if you have not completed scan(s) within 4 weeks of enrollment into this study. Some scans may need to be repeated for **research purposes**.

- You may have a CT scan, a PET/CT scan, or an MRI, (a magnetic resonance imaging scan) of different areas of your body (e.g. abdomen, pelvis) depending on where your disease is located and the type of symptoms you may have.
- You may have one MRI of you head with contrast.

Findings of unexpected changes in your disease may lead to additional testing to determine if you should be treated in a manner other than enrollment in this study.

If the screening tests show you are eligible, you will return to begin study treatment visits within 2 weeks.

RANDOMIZATION and STUDY TREATMENT (each visit will last between 2 and 5 hours):

You will be randomly assigned (like the flip of a coin) to 1 of 2 study treatment groups. You have an equal chance of being assigned to either of the study groups. Neither you nor your doctor can choose which group you are assigned. All groups will receive both the HIFU treatment and pembrolizumab. *The difference between the groups is the timing of the first dose of pembrolizumab.*

GROUP 1: HIFU treatment on day 15 of cycle 1
200mg Pembrolizumab IV (study drug) given on day 1 of every 3 week cycle starting on day 1 of cycle 2 for up to 2 years.

GROUP 2: HIFU treatment on day 15 of cycle 1
200mg Pembrolizumab IV (study drug) given on day 1 of every 3 week cycle starting on day 1 of cycle 1 for up to 2 years.

Note: 1 cycle=21 days

Pembrolizumab Administration and Blood Collection

You will be assessed to determine the most appropriate means by which the pembrolizumab will be administered (and/or other fluids given to you) and blood collected; this is typically a line (tube) placed in a vein in your body. Because the line that is used to administer your study drug cannot be used to collect study-related research bloods, you may have more than one line for use during the study. After you are enrolled in the study, these lines may be placed as part of your clinical care. A combination of types of lines may be used, such as IV, central, peripherally inserted central catheter (PICC or PIC), peripheral, and/or possible short-arm port(s) or central venous access (see below).

The types of lines used may change during the course of the study, and you may have multiple lines placed/replaced for use during the study.

Central Venous Access Placement, Pre-treatment visit

After you are enrolled you may be required to return to UVA to have a central venous access catheter/device placed, also known as a port. If so, this procedure will be done as part of your clinical care.

A *Central Venous Access* (CVA) uses a soft tube that will be inserted under your skin and into a large vein that leads to your heart. The CVA will allow the study drugs to be given directly into your blood stream. The CVA may also be used for blood collections during the study.

CVA placement will be done by a surgeon or radiologist during a short operation under local anesthesia in an out-patient setting or under anesthesia in an operating room. You may also receive pain medication afterwards to help keep you comfortable.

The timing of the CVA placement visit will vary and will depend on the availability of the CVA room to be used and CVA staff. You will be notified of the time and date. A member of the CVA team will discuss with you the procedures and risks; a separate standard hospital consent will be provided to you to read and sign. At the end of your participation in this study, the CVA may be removed.

For All Groups (Groups A and B) the following procedures will be completed at various times throughout the study. A study calendar is provided at the end of this section so that you can see the days that each of the following events occurs:

- You will receive pembrolizumab for **research purposes** on Day 1 of every cycle (except Arm A will not receive pembrolizumab on Cycle 1, but will start on Day 1 of cycle 2). Pembrolizumab will be given by infusion into a vein over 30 minutes.

- You will receive the HIFU treatment of your breast tumor for **research purposes** on Day 15 of cycle 1:
  - For women, if you can get pregnant a pregnancy test will be completed.
  - An IV catheter will be placed in a vein in your arm. An IV catheter is a small flexible tube in your blood vessel guided by a needle. Once the tube is in place the needle is removed and replaced with a cap that allows medication to be given. During the HIFU procedure you will be in a state of conscious sedation, which is combination of medicines to help you relax (a sedative) and to block pain (an anesthetic). You will probably stay awake but may not be able to speak. You will sign a separate consent for the sedation procedure.
  - You may also have a **pulse oximeter** (small plastic device that slips over your finger to measure your oxygen level and heart rate during the HIFU treatment)
  - You will be asked about your breast pain prior to and immediately following the HIFU procedure.
  - You will be positioned for the procedure so that the HIFU beam can be directed to the tumor in your breast. You will need to lie still during the procedure (which may take an hour or more depending on the size of the area to be treated).
  - Your doctor may use a clamp-like device to help stabilize your breast during the procedure which will help hold the tissue still.
  - A series of sound waves will be focused on the tumor within your breast to cover the planned target area. An ultrasound will be used to guide the beam of the HIFU to the targeted site.
  - Once the procedure is complete, ice may be applied to the HIFU treated area.
  - Once you are awake and ready, you will be allowed to go home. You must have someone to drive you home after your HIFU procedure.

- You will have a physical exam (similar to the exam completed at screening) and your vital signs will be collected. We will review medications any health problems you may have experienced

since your last visit. These procedures will be completed on day 1 of every cycle as part of your clinical care.

- You will be asked about your breast pain following the HIFU treatment (Cycle 2) for **research purposes**.

- You will have a biopsy of your HIFU treated breast tumor on day 1 of cycle 1 and day 1 of cycle 2. The biopsies may require ultrasound or CT guidance. These biopsies are required and will be completed for **research purposes**.

- If you agree to have optional biopsies, you may have a biopsy of the HIFU treated tumor and a different tumor during your cycle 4 visit. The biopsies may require CT guidance. These biopsies will be optional and completed for **research purposes.**

- About 1 to 2 tablespoons of blood will be drawn from a vein in your arm to perform the following tests:
    - Check your blood counts, LDH, certain levels of fats, salts, and sugars, kidney and liver function, and your immune cell counts. These will be completed on Day 1 of every cycle as part of your clinical care.
    - Check how well your blood clots. These tests will be completed on day 1 of cycles 2, 3, 4, and 5 for **research purposes.**
    - Check your thyroid function. These tests will be completed on day 1 of cycles 1, 2, 4, and every even cycle after for **research purposes**.
    - For women: if you can get pregnant you will have a pregnancy test done for **research purposes** (Groups A & B at screening, Group A also on day 1 of cycle 2).

- Your urine will be tested on day 1 of cycles 1, 3, 5, 7 and every odd cycle after to check your kidney function. This test will be completed for **research purposes**.

- About 3 tablespoons of blood will be drawn from a vein in your arm to study your immune system. These blood tests will be completed on day 1 of cycles 1, 2, 3 and 4 for **research purposes**.

- Scans of your tumor will be performed about every 4 cycles as part of your clinical care.

We will give you a diary so that you can keep track of any symptoms or side-effects that you may experience over the course of the study. The diary will be completed for **research purposes**.

FOLLOW UP:

All participants will have an end of treatment visit when they discontinue study treatment and a safety follow-up 30 days later. You may remain in study follow-up for up to 2 years after beginning study treatment, with follow-up study visits every 3 months. At these visits, the following procedures may be completed:

- You will have a physical exam (similar to the exam completed at screening) and your vital signs will be taken by a clinician. We will review your medications and any health problems you may have experienced since your last visit. These procedures will be completed at treatment discontinuation and at 30 days follow up as part of your clinical care.

- We will review your diary of symptoms and side-effects that you may experience during follow-up. This will be completed for **research purposes**.

- About 1 tablespoon of blood will be drawn from a vein in your arm to check your blood counts, LDH, certain levels of fats, salts, and sugars, thyroid, pancreas, kidney and liver function, and your immune cell counts. These tests will be completed at study discontinuation and at 30 days follow up only, and will be part of your clinical care.

- Scans of your tumor will be performed as part of your clinical care if you have not completed scan(s) within 8 weeks**.**

We would like to know about other cancer treatment you receive and keep track of your medical condition for the rest of your life or until the study is completed. We would like to do this by calling you on the telephone once a year to see how you are doing. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study.

Second Course Treatment (for all Groups A and B)

If your disease responds well to study treatment and progresses after stopping pembrolizumab, you may be eligible for up to one year of additional pembrolizumab. Your study doctor will determine if you meet the study criteria to be eligible for the Second Course treatment. If you are eligible, you will restart treatment and will be retreated with pembrolizumab at the dose and dose frequency that you received during your last treatment course.

Note: When you begin the second course treatment, the numbering of your treatment cycles will re-start with cycle 1.

The following procedures will be completed during the second course treatment:

- You will have a physical exam (similar to the exam completed at screening) and your vital signs will be taken by a clinician. We will review your medications and any health problems you may have experienced since your last visit. The will be completed on day 1 of every cycle as part of your clinical care.
- About 1 tablespoon of blood will be drawn from a vein in your arm to check your blood counts, LDH, certain levels of fats, salts, and sugars, thyroid, pancreas, kidney and liver function, and your immune cell counts. These tests will be completed as part of your clinical care.
- For women: Perform a pregnancy test if you can get pregnant. This will be performed for research purposes.
- Your urine will be tested every even cycle to check your kidney function. This test will be completed for **research purposes**.

- Scans of your tumor will be performed as part of your clinical care about every 4 cycles.
- We will give you a diary to keep track of any symptoms or side-effects that you may experience over the course of the study. This will be completed for **research purposes**.
- Pembrolizumab will be given by infusion into a vein over 30 minutes **for research purposes**.

Once you complete the second course treatment you will return to the clinic for an end of treatment visit and follow-up visits as described above.

What are your responsibilities in the study?

You and your parent/legal guardian have certain responsibilities to help ensure your safety. These responsibilities are listed below:

- You must come to each study visit.
- You must be completely truthful about your health history.
- Follow all instructions given.
- You should tell the study doctor or study staff about any changes in your health or the way you feel.
- Answer all of the study-related questions completely.
- Inform the study doctor or study staff as soon as possible if you have to take any new medications, including anything prescribed by a doctor or those that you can buy without a prescription (over-the-counter), including herbal supplements and vitamins. The study doctor will let you know if you can take these medications.

Specimens

Blood testing

We will take (or "draw") up to 17 tablespoons of blood over the first 3 months or 4 cycles of study treatment. If you continue to receive study treatment through the entire two year study treatment period, the maximum total amount of blood we will take will be about 47 tablespoons.
Up to 15 additional tablespoons of blood may be drawn during the second course treatment if you qualify and are treated through the maximum one year second course treatment period.
The blood we take will be tested to:

- Check your blood counts, LDH, certain levels of fats, salts, and sugars, thyroid, pancreas, kidney and liver function, and your immune cell counts.
- Check how well your blood clots.
- Test for HIV and Hepatitis B and Hepatitis C virus.
- For women: Perform a blood pregnancy test.
- Research testing to study your body's immune response to HIFU and pembrolizumab.

Tumor Specimens

We will take or collect up to 3 biopsies of your tumor. The tumor will be tested to study your body's immune responses to HIFU and pembrolizumab.

Study Calendars

Procedures and Tests		Active Study Treatment									Follow-up		
Day	Screen-ing	1	15	22	43	64	85	106	127	148	End of Treatment	30 days after last treatment	Every 3 months up to 2 years
Cycle (3 weeks)		1		2	3	4	5	6	7	8			
Informed Consent	X												
Medical History	X												
Pathology review	X												
Physical Exam/vital signs	**X**	**X**		X	**X**	X	X	X	X	X	X	X	
Ultrasound	**X**												
Pain Assessment			**X**	**X**									
Clinical blood tests	**X**	**X**		X	**X**	X	X	X	X	X	X	X	
Blood tests for research		**X**		**X**	**X**	**X**							
Urine Test		**X**			**X**		**X**		**X**				
Pregnancy Test	**X**		**X**	**X[A]**									
Required Biopsy		**X**		**X**									
Optional Biopsies						**X**							
HIFU procedure			**X**										
Pembrolizumab		**X[B]**		**X**	**X**	**X**	**X**	**X**	**X**	**X**			
Symptom Diary (review & distribution)		**X[B]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Scans	X[#]					X				X	X[^]		
Other therapies													**X**

Note: additional odd # cycles beyond cycle 8 will have the same activities as cycle 7. Additional even # cycles will have the same activities as cycle 8.

Bold text indicated for research purposes

[A] Procedure for Arm A only. [B] Procedure for Arm B only.

[#] If you have had scans recently but another scan is necessary for eligibility screening, an extra CT scan and/or MRI may need to be done and would be considered **for research purposes**.

^Scans are to be completed about every 12 weeks (4 cycles) as part of your clinical care. If you have had scans completed as part of your clinical care within 8 weeks, you would not be required to have repeat scans at the end of treatment visit.

Procedures and Tests	Second Course Treatment							
Day	1	22	43	64	85	106	127	148
Cycle	1	2	3	4	5	6	7	8
Physical Exam/vital signs	X	X	X	X	X	X	X	X
Clinical blood tests	X	X	X	X	X	X	X	X
Urine Test	**X**		**X**		**X**		**X**	
Pembrolizumab	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Symptom Diary (review & distribution)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Scans*								

Note: additional odd # cycles beyond cycle 8 will have the same activities as cycle 7. Additional even # cycles will have the same activities as cycle 8.

Bold text indicated for research purposes

*Scans are to be completed approximately every 12 weeks or every 4 cycles as part of your clinical care.

If you want to know about the results before the study is done:

During the study you are having an investigational test done. The purpose of the test is NOT to diagnose any disease or abnormality you may have. Because the test is investigational there is no way for the study leader to understand if the results are "normal" or "abnormal". However, IF any test results are concerning, your study leader will let you know. In addition, as the research moves forward, your study leader will keep you informed of any new findings about the research itself that may be important for your health or may help you decide if you want to continue in the study. The final results of the research will not be known until all the information from everyone is combined and reviewed. At that time you can ask for more information about the study results.

Optional Collection of Samples and Health Information for Specimen Banking

What Sort of Research Will Be Done On Your Sample(s)?

You are being asked to provide leftover samples of your blood and tumor tissue to be used for research. Along with specimens, researchers may need to collect some health information about you. Combining information from the specimen with information from your health records may be useful for this research. For this research, the following types of information could be included: diagnosis, treatment, age, gender, sample type.

If you agree, leftover specimens collected for research will be added to a research specimen bank. The purpose of a specimen bank is to process, and store samples until researchers need them for future research. The long term goals of the samples collected in this bank will be mainly used for research on breast cancer. Is it not possible, however, to list every research project that will include the samples because we cannot predict all of the research questions that will be important over the coming years. As we learn more, new research questions and new types of research may be done.

Your specimen sample may be used to create a living specimen sample (called a "cell line") that can be grown in the laboratory. This allows researchers to have an unlimited supply of your cells in the future without asking for more samples from you.

Researchers may do genetic research on the DNA in your specimen sample. DNA is the material that makes up your genes. All living things are made of cells. Genes are the part of cells that contain the instructions which tell our bodies how to grow and work, and determine physical characteristics such as hair and eye color. Genes are passed from parent to child.

What will you have to do to give samples for research?

Your doctor will obtain blood and tumor tissue from you for research testing. These samples will be collected as part of the research study at the time points described above. There may be samples left over. Normally, these leftover samples would be thrown away. We are asking you to allow us to collect this leftover material for specimen banking.

How Will Your Sample(s) Be Labeled?

Your sample(s) will not be labeled with your name or other information that would identify you directly. Instead, it will have a unique code that allows for it to be linked to some of your health information. This

link means that your specimen can be identified but only indirectly. We can find out if we need to know which sample is yours in the event you wish the sample to be removed at a later date

How Will Your Sample(s) Be Stored and Labeled for Specimen Banking?
Dr. Craig Slingluff, the director of the UVA Human Immune Therapy Center (HITC) will be responsible for storing your sample and for protecting your privacy.

This research specimen bank is located at the University of Virginia under the leadership of Dr. Slingluff. There is no set limit to the number of people who will provide samples to this bank.

Your sample(s) will not be labeled with your name or other information that would identify you directly. Instead, it will have a unique code that allows for it to be linked to some of your health information. This link means that your specimen can be identified but only indirectly. We can find out if we need to know which sample is yours in the event you wish the sample to be removed from the bank later.

Which researchers can use your samples and what information about you can they have?
Your sample may be shared with researchers at the University of Virginia and at other institutions. Dr. Slingluff will not give your name to other researchers who want to use your sample, but will only give them information like your age and what disease/condition you have. Those who would see the information would include researchers and the others listed under "Who will see your private information?" section of this consent document.

Some of the people who receive your information may not have to follow the privacy laws and may share or release your information because they do not have to follow the privacy laws.

What Are the Benefits To Donating Your Sample(s) For Specimen Banking?
The specimen banking that is done with your sample is not meant to help you. But, doctors hope that in the future it will help people who have other diseases or conditions.

It is very unlikely that any future research (specimen banking) performed using your specimen(s) would benefit you directly, but it may provide important medical knowledge that could help other patients with your medical condition or other medical problems in the future.

What Are The Risks of Donating Your Sample(s) For This Study?

<u>Risks to Privacy from Specimen Banking:</u>
The main risk of allowing us to store and use your samples and certain limited health information for research is a potential loss of privacy. One of the risks to you is the release of information from your health records. The University of Virginia will do its best to protect your records so that facts about you and your health will be kept private. The chance that information identifying you will be given to someone else is very small. However, we cannot *guarantee* it will be safe. To further safeguard your privacy, information obtained from future research will not be placed in your medical record.

There are certain risks of having health information given to other people by mistake. In the unlikely event that this happens, it could cause discrimination or mental harm to you or your family members if others were to see this information. The results could be that you may not be able to get or keep certain kinds of insurance. It could also hurt family relationships.

Your doctor will explain the risks of the routine medical procedure you are having. In some cases, your doctor will ask you to sign a separate clinical consent form that explains the risks of the procedure. Allowing your samples to be placed in the bank for future research will not change the risks of the medical procedure itself.
Because everyone has unique DNA, it is also possible, although very unlikely, that someone could identify you through your DNA if they have another sample of your DNA.

Different types of genetic tests carry different levels of risks. Depending upon the type of research that is completed on your banked specimens, information about your genetic make-up could mean that you and your family members may face problems that could lead to getting or keeping some kinds of insurance or affect your ability to get or keep a job. To keep this from happening, the results of these tests will not be given to anyone outside of the study staff. There is no way to predict all the possible risks of this research.

Will You Find Out the Results of the Research on Your Sample(s) for Specimen Banking?
Neither you, your health care provider**,** nor anyone in your family, will receive the results of any research done on your sample(s). The results will not be put in your health records. Therefore, results from any research done on your sample(s) will not affect your medical care. This helps protect you and other members of your family from harm that might be caused by this information.

What If You Change Your Mind About Donating Your Sample(s) for Specimen Banking?
If you decide now that your sample(s) can be kept for specimen banking, and later change your mind, you can simply withdraw the sample(s) at that time. To withdraw you will need to write to the Principal Investigator listed on the first page of this form. We will then destroy any of your tissue that has not already been used. However, if your sample has been used in genetic research, the information that we have learned will remain in the study, even if you withdraw. Unless you withdraw from the study, permission for researchers to use your tissue and to use and share your private health information for this study will never end.

Will You Be Paid For Donating Your Sample(s) for Specimen Banking?
You will not be paid to donate your sample(s) for specimen banking.

Will Donating Your Sample(s) Cost You Any Money?
There is no cost to you to have your samples collected or used for specimen banking.

Specimen Banking Options:

You do not have to participate and agree for specimens to be collected for specimen banking in order to be in the main part of this study. No matter what you decide to do, your decision will not

affect your medical care. You can tell us your choice by placing your initials in one of the options below:

SPECIMEN BANKING:
Please indicate your choice by placing your initials below:

___ YES, Your sample(s) may be saved for future research and stored in a specimen bank.

___ NO, Your sample(s) may NOT be saved for future research and stored in a specimen bank.

What are the risks of being in this study?

Risks related to High Intensity Focus Ultrasound Treatment

Common Side Effects

- Swelling: subcutaneous edema (increased fluid under the skin surrounding the tumor). This minor risk is brief and usually solved with local application of ice. In most cases, the swelling goes away during the 24 hours after the treatment.
- Pain: to minimize pain and discomfort, HIFU treatment may be delivered under conscious sedation, which is a combination of medicines to help you relax (a sedative) and to block pain (an anesthetic) or general anesthesia.

Less Common Side Effects

- Treatment area damage which could include the following:
  - Bruising – very infrequent
  - Skin irritation (temporary redness) – lasted briefly and resolved without treatment
  - Scar (like a moderate skin burn) – very infrequent
  - Abscess formation in the breast (collection of pus that builds up within the tissue of the body)– one case reported.
  - Fibrosis and/or induration (i.e., increase in fibrous tissue that may feel hard on physical exam) – one case that was persistent (continuous) has been observed in pilot clinical studies to date; no other patients experienced treatment area damage that was more than transient (lasting a short time)
  - Skin pigment change over the treated area - in one case out of 89, an irregularly shaped light brownish darkening of skin was visible at a 6 month follow-up.
  - A burn to the skin: it is believed that the risk of skin burn is very low. In a European study with 89 consecutive treatments only 5 instances occurred, all of which resolved in 10 days. In other studies, no instances of skin burn were reported.

Other possible risks that have not been seen to date:

- Damage to the rib cage: the beam energy will be directed so that it does not reach the rib cage, so no damage to the rib cage is expected.
- Damage to the lung: The beam energy will be directed so that it does not reach the lung, so no damage to the lung is expected.

- Nerve damage / Skin dysesthesia (an unpleasant sense of touch)
- Possible damage to lactation ducts that could potentially lead to difficulty breast feeding.
- Permanent deformity of the breast
- Skin ulceration - an open sore on the skin
- Cellulitis - bacterial skin infection that appears as a swollen, red area of skin that feels hot and tender.

Risks Related to the sedation medications (used for conscious sedation and general anesthesia) during the HIFU procedure:

Common Side Effects

- Groggy feeling or dizziness for up to 12 hours after sedation medication.
- Headache
- Pain, swelling and/or bruising at the IV site

Less Common Side Effects

- Changes in blood pressure (too high or too low), changes in heart rate (too low), or slowed breathing rate during sedation.
- Nausea, vomiting, digestive troubles (heartburn or stomach aches), or constipation
- Irritation of the vein, called phlebitis, where the needle was placed, which may progress up the arm and potentially effect hand or arm motion temporarily and may require additional treatment.

Rare But Serious Side Effects

Sedation is a serious medical procedure that has rare but serious risks which could include:

- Allergic reaction to the medications
- Heart attack
- Stroke
- Brain damage
- Death

Risks Related to Pembrolizumab/Keytruda®

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Very common, some may be serious (i.e. causing hospitalization, life-threatening or where noted, may cause death) side effects (at least 20 out of 100 participants experienced)

- Itching of the skin
- Loose or watery stools
- Cough

Common, some may be serious (i.e. causing hospitalization, life-threatening or where noted, may cause death) side effects (5 to 20 out of 100 participants experienced)

- Joint pain
- Fever
- Back pain
- Rash
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone. So you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism).
- Low level of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or sick to your stomach (hyponatremia)

Uncommon, some may be serious (i.e. causing hospitalization, life-threatening or where noted, may cause death) side effects (1 to 5 out of 100 participants experienced)

- Inflammation of the lungs, so you may feel short of breath and cough (pneumonitis).
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus (colitis)
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e., peeling, itching, and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye, and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection (Severe skin reactions, including Stevens-Johnson syndrome/or toxic epidermal necrolysis).

Rare, some may be serious (i.e. causing hospitalization, life-threatening or where noted, may cause death) side effects (less than 1 out of 100 participants experienced)

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome)
- Inflammation of the muscles so you may feel weakness or pain in the muscles (myositis)
- Inflammation of pancreas (a gland in your abdomen that controls sugar levels), so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)

- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness, or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination, and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney, so you may pass less urine or have cloudy urine, or bloody urine, swelling, and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath, and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting (myocarditis). Sometimes this condition can lead to death
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy (thyroiditis)
- A condition that may make you feel week and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis). Symptoms will depend on the particular blood vessels that are involved in the inflammatory process, for example; if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue.
- Low levels of parathyroid hormone (a hormone made by 4 tiny glands in your neck) which may result in low blood calcium and cause muscle cramps or spasms; fatigue or weakness; numbness, tingling or burning in your fingertips, toes or lips (hypoparathyroidism).

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis).
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in the right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, **after receiving pembrolizumab**. Sometimes this condition can lead to death.

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant that you have had.

Risks related to tumor biopsies

Likely

- Discomfort from insertion of the needle for local anesthetic
- Pain
- Scar at the biopsy site
- Bruising and mild discomfort at the biopsy site
- Numbness at the biopsy site
- Swelling at the biopsy site
- Bleeding at the biopsy site
- Small wound which may take a few weeks to heal

Rare

- Infection at the biopsy site

Risks from CT scans for Research

This study may involve radiation exposure from a computed tomography (CT) scan, a CT guided biopsy and Chest X-ray. Although each organ will receive a different dose, it is estimated that the maximum total effective radiation dose you could receive from these exams is believed to be 26 mSv. For comparison, this dose is roughly 50% the annual radiation dose safely allowed for a radiation worker such as the person performing your CT. This radiation dose is what you could receive from the research part of this study only and does not include any additional CT's or imaging you may have received or will likely receive from tests that are Standard of Care. The precise risk from this dose is not known but is thought to be small. This radiation exposure is not necessary for your medical care but is necessary to obtain the research information desired. If you are pregnant, you may not participate in this research study. It is best to avoid radiation exposure to unborn children since they are more sensitive to radiation than adults.

Risks of having an MRI

You may have an MRI as part of this study. MRI scanning is a painless procedure that only requires that you lie quietly on a padded table that gently glides you into a large magnet.
While the scanner is performing your scan, you will hear some humming and thumping sounds. These are normal and should not worry you. Because of the magnetic field and radio frequencies people with any type of metal in their body should NOT have an MRI. This may include things like pacemakers, aneurysm clips or shrapnel. It is important that you inform the technologist if you have any of these metallic appliances. Please inform the technologist if you are pregnant or think that you may be pregnant.
There is a low risk of experiencing symptoms of anxiety or claustrophobia while lying in the scanner. Should you experience these symptoms or otherwise become uncomfortable you can voluntarily stop your participation in this study. There will be NO consequences to your clinical care or to your participation in the study should you choose to stop your participation.

Risk of using gadolinium:

You may receive a contrast called Gadolinium if you have an MRI/MRA. This substance will help the tissues show up better.

The following risks are associated with gadolinium contrast:

- Allergic reaction. Some people experience temporary itching after receiving MRI contrast. Less than one person in 300,000 will experience severe allergic reaction which requires treatment. Severe allergic reaction may include s difficulty breathing or wheezing, tightness in the throat, swelling of lips, tongue or throat, fast heartbeat.
- Contrast infiltration. Contrast that is injected outside the vein into other tissues can cause local pain and swelling at the injection site. Treatment generally consists of hot or cold packs and elevation of the affected arm. Infiltrations most often get better over time.
- Temporary metallic taste in the mouth, tingling in the arm, nausea, or headache occurs in less than 1 in 100 people.
- The FDA has received information about an extremely rare disease called Nephrogenic Systemic Fibrosis (NSF) is a rare disease that is linked with the use of Gadolinium in people with severe kidney disease.

NSF causes hardening and thickening (fibrosis) of the skin, connective tissues like muscles, tendons, ligaments, and blood vessels throughout the body. In addition, those who develop NSF may have scarring of their body organs. The signs of NSF also include:

- burning, itching, swelling, hardening and tightening of skin;
- red or dark patches on the skin;
- yellow spots on the whites of the eyes;
- stiffness in joints with trouble moving or straightening the arms, hands, legs or feet;
- pain deep in the hip bones or ribs;
- Muscle weakness.

In most of the cases reported to the FDA, symptoms of NSF started between 2 days to 18 months after a person received the Gadolinium-based contrast agent. NSF may get worse and may lead to death. There is no known treatment for NSF.

If you have any of the symptoms listed above after receiving Gadolinium-based contrast for a study MRI/MRA, please contact the study team immediately. The study team will review your symptoms and perhaps recommend a skin biopsy, which is the only way to determine if you actually have NSF.

The FDA has received information indicating that gadolinium may deposit in the brain and other organs of some people who have had four or more gadolinium contrast-enhanced MRI scans and it may remain for a long time. Although no signs or symptoms of negative health effects or changes to organs have been seen with these deposits to date, it is not known if these deposits may lead to negative health effects in the future.

Before you receive gadolinium/additional gadolinium for research:

- You will be screened by UVa Department of Radiology staff prior to getting gadolinium. If radiology screening shows that it might be unsafe for you to receive this contrast, then you will not be able to receive the contrast.

Blood Donation

If you participate in this study it may affect your ability to donate blood. If you have any questions call the organization where you donate blood and talk to one of their nurses.

Risks of having your blood drawn

Having blood drawn may cause:

- ✓ pain (common),
- ✓ a bruise (sometimes),
- ✓ fainting or passing out (not very often), and
- ✓ infection (rare).

If the people doing the study are exposed to your blood or body fluids in a way that could give them a disease, your blood may be tested. The tests might check for:

- ✓ hepatitis,
- ✓ HIV (Human Immunodeficiency Virus), or

- ✓ other infections.

You and the person exposed would be told the test results. However, your name would be kept private. If your test is positive for hepatitis or HIV or any other infection that may affect your clinical care, we will tell you the results and help you understand what the results mean for you.

A caution about giving too much blood:
Because of the amount of blood being taken, you should not give blood for other reasons until you have finished your participation in this study. For example, avoid giving blood at a blood bank or in another research study.

Risks of taking blood from an IV catheter:
Risk of Repeated Sticks
Sometimes the catheter stops working. In order to get the blood we need, we may have to stick you again with another needle.

Risks for women:
Pregnancy and Contraception
The drug(s) used in this study can harm an unborn or nursing baby. Therefore, you cannot be in this study if you are pregnant or nursing a baby. A pregnancy blood test will be done about 14 days before starting this study if you are a woman able to become pregnant. You MUST NOT become pregnant while on this study or for at least 4 months after your last dose of pembrolizumab.
You and your partner must use an approved form of birth control during this study. Examples of birth control you may use are:

- Norplant
- IUD (intrauterine device)
- Depo-Provera
- Birth Control Pills
- Birth Control Patch
- Sterilization

The birth control methods listed below are less effective. They may be used if combined with other birth control methods:

- Condoms
- Jellies or foam
- Withdrawal
- Sponge
- Diaphragm
- Rhythm
- Cervical cap

Ask your doctor for more details about the proper birth control method for you. If you become pregnant during this study, you must tell your doctor right away. Your doctor will discuss your treatment and the effect on the pregnancy.

Risks for men:
We also do not know the effects of these drugs on male sperm. If you are a male, you should not father a baby while you are in this study or for at least 4 months after your last dose of the pembrolizumab. You should also not donate to a sperm bank during this time. To do so may hurt your

unborn baby. Use an effective method of birth control during this time. Effective forms of birth control are listed above).

If your partner becomes pregnant during this study, you must tell your doctor right away. The study team will ask to contact her to obtain her consent to obtain information about the baby after it is born. She will be asked to sign a "***Pregnancy Follow-up/Release of Information Addendum***".

Other unexpected risks:
You may have side effects that we do not expect or know to watch for now. Call the study leader if you have any symptoms or problems.

Could you be helped by being in this study?

You may or may not benefit from being in this study. Your immune system may become activated against your tumor; however, we cannot guarantee that this will happen or that you will benefit in any way by participating in this study. Information researchers get from this study may help others in the future.

What are your other choices if you do not join this study?

You do not have to be in this study to be treated for your condition. You can get the usual treatment even if you choose not to be in this study. Other possible treatments may include:

- Chemotherapy
- Hormonal therapy
- Surgery
- Another experimental therapy
- Palliative care or comfort care, which is not meant to treat your condition, but helps you feel more comfortable

If you are an employee of UVa your job will not be affected if you decide not to participate in this study. If you are a student at UVa, your grades will not be affected if you decide not to participate in this study.

Will you be paid for being in this study?

You will not get any money for being in this study.

By agreeing to be in this study, you are donating your blood and tissue samples for research, and giving up any property rights you may have in them. The results of this research using your donated materials may have commercial value. However, you will not receive any payments.

Will being in this study cost you any money?

The following procedures/tests, will be provided at no cost to you or your health insurance:

- HIFU procedure
- Ultrasound of the breast during screening
- Pembrolizumab study drug and administration
- Biopsies done for research purposes

- Blood draws for research purposes to test your immune system
- Clinical blood draws/tests that include the following:
  - HIV, Hepatitis B and Hepatitis C virus
  - check how your blood clots
  - check your thyroid function
  - check your blood counts, levels of fats, salts, sugars, kidney and liver function, immune cell counts at screening visit, and day 1 of cycles 1 and 3 only
  - pregnancy tests
- Urine tests
- Symptom diary review and administration
- Physical exams for screening, and day 1 of cycles 1 and 3 only
- If additional scans that are outside of your standard clinical care are necessary at the screening visit, the scans performed for **research purposes** will be paid for by the study.

You and/or your insurance company must pay for any tests or care given beyond what is required in this study. In addition, you and/or your health insurance may also have to pay for other drugs or treatments that are given to help you control any side effects. You will have to pay for any costs not covered by your health plan. You may be responsible for any co-payments or deductibles. You may wish to ask your insurance company for an estimate of what these costs might be or if pre-approval is required.

You will be responsible for the cost of travel to come to any study visit and for any parking costs.

What if you are hurt in this study?

You do not give up any legal rights, such as seeking compensation for injury, by signing this form. If you feel you have been injured as a result of this study you may contact the Principal Investigator or the IRB (phone numbers are located near the end of this form). If you are hurt as a result of being in this study, there are no plans to pay you for medical expenses, lost wages, disability, or discomfort. The charges for any medical treatment you receive will be billed to your insurance. You will be responsible for any amount your insurance does not cover.

What happens if you leave the study early?

You can change your mind about being in the study any time. You can agree to be in the study now and change your mind later. If you decide to stop, please tell us right away. You do not have to be in this study to get services you can normally get at the University of Virginia.

Even if you do not change your mind, the study leader can take you out of the study. Some of the reasons for doing so may include

a) Your study physician is concerned about your health
b) Your disease gets worse
c) The side effects of the treatment are too dangerous for you
d) New information shows the treatment will not work or is not safe for you
e) You do not follow your doctor's instructions
f) The study sponsor closes the study for safety, administrative or other reasons

If you decide to stop being in the study, we will ask you to notify the Principal Investigator as soon as possible.

How will your personal information be shared?

The UVa researchers are asking for your permission to gather, use and share information about you for this study. If you decide not to give your permission, you cannot be in this study, but you can continue to receive regular medical care at UVA.

If you sign this form, we may collect any or all of the following information about you:

- Personal information such as name, address and date of birth
- Social Security number ONLY IF you are being paid to be in this study
- Your health information if required for this study. This may include a review of your medical records and test results from before, during and after the study from any of your doctors or health care providers. This may include mental health care records, substance abuse records, and/or HIV/AIDS records.
- Tissue or blood samples if you agree to provide them for genetic testing for this study

Who will see your private information?

- The researchers to make sure they can conduct the study the right way, observe the effects of the study and understand its results
- People or groups that oversee the study to make sure it is done correctly
- The sponsor(s) of this study, and the people or groups it hires to help perform or review this research
- Insurance companies or other organizations that may need the information in order to pay your medical bills or other costs of your participation in the study
- Tax reporting offices (if you are paid for being in the study)
- People who evaluate study results, which can include sponsors and other companies that make the drug or device being studied, researchers at other sites conducting the same study, and government agencies that provide oversight such as the Food and Drug Administration (FDA) if the study is regulated by the FDA. This also includes Theraclion, the company that is providing the Echopulse device. A representative from Theraclion may be in the procedure room during the Echopulse treatment to oversee the procedure or available for technical support via telemedicine procedures such as WebEx.
- If you tell us that someone is hurting you, or that you might hurt yourself or someone else, the law may require us to let people in authority know so they can protect you and others.

Some of the people outside of UVa who will see your information may not have to follow the same privacy laws that we follow. They may release your information to others, and it may no longer be protected by those laws.

The information collected from you might be published in a medical journal. This would be done in a way that protects your privacy. No one will be able to find out from the article that you were in the study.

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.

What if you sign the form but then decide you don't want your private information shared?

You can change your mind at any time. Your permission does not end unless you cancel it. To cancel it, please send a letter to the researchers listed on this form. Then you will no longer be in the study. The researchers will still use information about you that was collected before you ended your participation.

A copy of this consent form will be put in your medical record. (This is not the same as the record of this research study.) This means that everyone who is allowed to see your medical records will be able to find out that you are in this study. This is done so your regular doctors will know what you receive as part of this study. If you have other health problems during the study, they will be able to treat you properly.

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: **Patrick Dillon, MD**
PO Box 800716
University of Virginia
Charlottesville, VA 22908 Telephone: (434)982-1495

What if you have a concern about this study?

You may also report a concern about this study or ask questions about your rights as a research subject by contacting the Institutional Review Board listed below.

University of Virginia Institutional Review Board for Health Sciences Research
PO Box 800483
Charlottesville, Virginia 22908 Telephone: 434-924-9634

When you call or write about a concern, please give as much information as you can. Include the name of the study leader, the IRB-HSR Number (at the top of this form), and details about the problem. This will help officials look into your concern. When reporting a concern, you do not have to give your name.

Signatures

What does your signature mean?

Before you sign this form, please ask questions about any part of this study that is not clear to you. Your signature below means that you have received this information and all your questions have been answered. If you sign the form it means that you agree to join the study. You will receive a copy of this signed document.

Consent From Adult

_____	_____	_____
PARTICIPANT (SIGNATURE)	PARTICIPANT (PRINT)	DATE

To be completed by participant if 18 years of age or older.

If an interpreter is involved in the consent process because the potential subject does not speak English well or at all, the participant should NOT sign on the line above – leave this line blank. Instead, the participant should sign the Short Form or full consent written in the language they can understand.

Person Obtaining Consent

By signing below you confirm that you have fully explained this study to the potential subject, allowed them time to read the consent or have the consent read to them, and have answered all their questions.

_____	_____	_____
PERSON OBTAINING CONSENT (SIGNATURE)	PERSON OBTAINING CONSENT (PRINT)	DATE

Interpreter

By signing below you confirm that the study has been fully explained to the potential subject in a language they understand and have answered all their questions.

_____	_____	_____
INTERPRETER (SIGNATURE)	INTERPRETER (PRINT)	DATE

If an interpreter was used to explain this study to a potential subject, the interpreter must sign and date the line above.

Consent from Impartial Witness

If this consent form is read to the subject because the subject is blind or illiterate, an impartial witness not affiliated with the research or study doctor must be present for the consenting process and sign the following statement. The subject may place an X on the Participant Signature line above.

I agree the information in this informed consent form was presented orally in my presence to the **identified individual(s)** who has had the opportunity to ask any questions he/she had about the study. I also agree that the **identified individual(s)** freely gave their informed consent to participate in this trial.

Please indicate with check box the identified individual(s):

☐ Subject

_____	_____	_____
IMPARTIAL WITNESS (SIGNATURE)	IMPARTIAL WITNESS (PRINT)	DATE