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Are you participating in any other research studies? _____ Yes _____No

INTRODUCTION TO RESEARCH STUDIES

A research study is designed to answer specific questions, sometimes about a drug's or device's safety and effectiveness. Being in a research study is different from being a patient. When you are a patient, you and your doctor have a great deal of freedom in making decisions about your health care. When you are a research participant, the Protocol Director and the research staff will follow the rules of the research study (protocol) as closely as possible, without compromising your health.

PURPOSE OF RESEARCH

You are invited to participate in a research study testing the safety and efficacy of a new cancer drug.

Your participation in this study is entirely voluntary.

In this study, we aim to find out what the maximum safe dose of a drug called dichloroacetate (DCA) and how effective it is in treating your cancer. We will determine that by using PET scanning using a new tracer, [^{18}F]EF5, which measures tumor hypoxia. Hypoxia, meaning a lack of oxygen, has been associated strongly with a wide range of human cancers. Hypoxia occurs when tumor growth exceeds the ability of blood vessels to supply the tumor with oxygenated blood. EF5-PET may be a non-invasive way to make this measurement.

EF5 is a radioactive dye intended for use in conjunction with a PET scan. You may be familiar with a similar procedure called and FDG-PET, which is a standard scan used to see metabolically active tissue such as tumors. In FDG-PET, fluorodeoxyglucose (FDG), a type of radioactively labeled sugar, is injected into the patient and used as a tracer. The PET scanner is capable of detecting radioactive signals, allowing doctors to see where in the body the tracer accumulates. Since FDG is a type of sugar, it accumulates in most metabolically active cells, allowing them to be identified.

EF5-PET is a very similar approach to FDG-PET. Instead of FDG, EF5 is used as the tracer. Since EF5 accumulates in hypoxic tissue, EF5-PET will illuminate tissues with low oxygen levels, such as a hypoxic tumor. It is hoped that an EF5-PET will provide a noninvasive alternative for the measurement of tumor hypoxia that is just as accurate and reliable as current, invasive methods.

In this study, you will be treated with DCA and undergo 2 EF5-PET and 2 FDG PET scans to see if the drug is having effect on your cancer. We will also check markers of tumor hypoxia and pyruvate deydrogenase kinase (PDK) activity to correlate with the changes we see on the scans. This will involve blood draws, most of which will already be done as part of standard care and may involve a needle biopsy depending on its feasibility. Biomarkers are proteins or genes found in blood and tissue that are associated with various things, in this case, tumor hypoxia.

Your decision whether or not to participate will determine your treatment. You will not be offered this drug off protocol as it is not an approved standard-of-care therapy for your cancer. If you decide to participate, you are free to withdraw your consent, and to discontinue participation at any time without prejudice to you or effect on your medical care. If you decide to terminate your participation in this study, you should notify Dr. Daniel Chang at 650-724-3547.

This research study is looking for 20 patients with recurrent head and neck cancer. Enrollment will occur exclusively at Stanford Hospitals and Clinics, so Stanford University expects to enroll all 20 research study participants.

You were selected as a possible participant in this study because you a recurrent head and neck cancer without an accepted standard-of-care treatment and you meet the other eligibility requirements. These include:

- Diagnosis of recurrent head and neck cancer
- 18+ years of age
- No previous cancer therapy within last 2 weeks
- Not pregnant or nursing

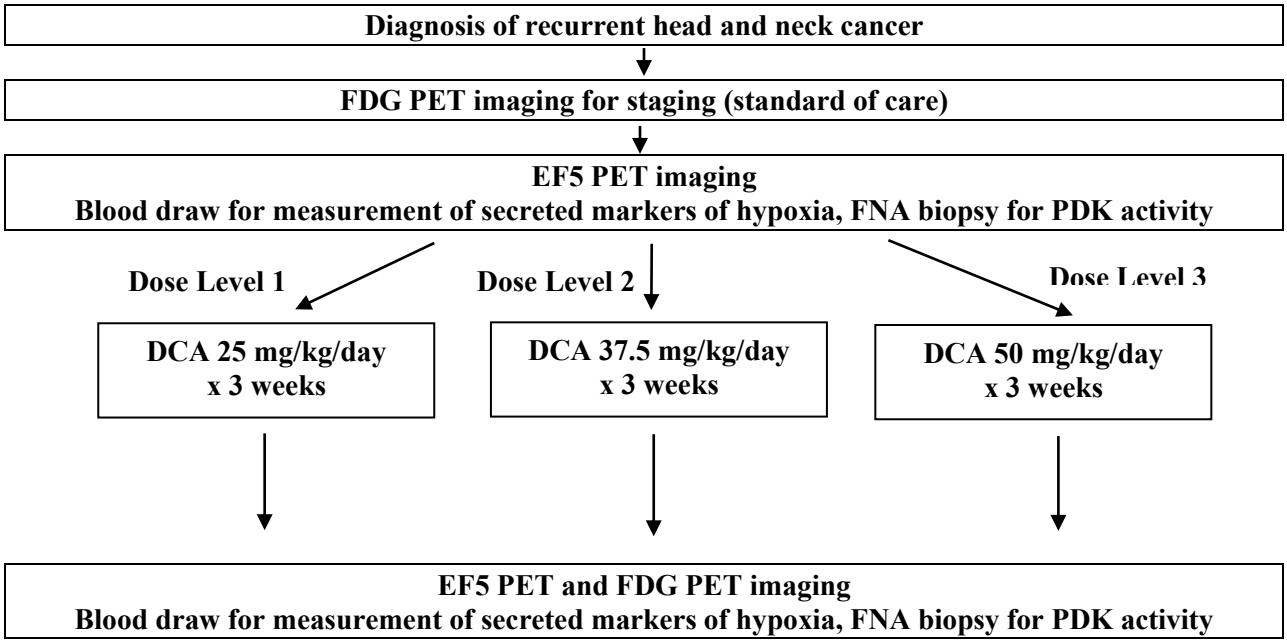
If you would like to participate, you also must:

- Have a physical examination completed 6 weeks prior to registration
- Women of childbearing potential, must complete a pregnancy test 2 weeks prior to registration (test result must be negative)
- Men, or women of childbearing potential must agree to practice effective birth control throughout the study period.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 1 year (to meet accrual goals); with approximately 3-4 weeks of active participation by each participant and quarterly follow-up appointments.

The following is an overall schematic of the study.



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PROCEDURES

If you choose to participate, Dr. Daniel Chang and his research study staff will need information from several screening tests, most of which are standard of care and will already have been done. The chart below details when each procedure will take place.

Study Calendar

	Pre-Enrollment[f]	Pre-Treatment[e]	Day 1-21	Day 20-Day 28	Follow-up[c]
EF5-PET[b]		Within 5 days of pre-treatment FDG-PET		Within 5 days of post-treatment FDG-PET	
FDG-PET[a]		Within 2 weeks prior to DCA treatment		Day 20-Day 30	
DCA			X		
Informed consent	X				
Demographics	X				
Medical history	X				X
Concurrent meds	X		X[h]		
Physical exam	X		X[h]		X
Vital signs	X		X[h]		X
Height	X				
Weight	X		X[h]		X
Pain Score	X		X[h]		X
Pain Medication Dosage	X		X[h]		X
Performance status	X		X[h]		X
FNA biopsy[d]		Within 8 weeks prior to DCA treatment		X	
Serum hypoxia biomarkers		Within 2 weeks prior to pre-treatment EF5-PET		X	
Serum chemistry + CBC w/ Diff	Within 4 weeks prior to enrollment	Within 2 weeks prior to DCA treatment		X	X
Adverse event evaluation	X		X[h]		X
CT or MRI or PET-CT	Within 8 weeks prior to enrollment				1 scan within 3 months post-tx
B-HCG	If applicable				
Other tests, as appropriate	X	X	X	X	X

a: To be done once Pre-treatment and once on Day 20-Day 30 of DCA trial
b: To be done within 1-5 days of the corresponding PET-CT scan
c: Follow-up at 4 weeks and 3 months post-treatment.
d: If feasible (depending on tumor location)
e: Treatment will ideally occur within 3 weeks of enrollment.
f: All pre-enrollment evaluations must have been completed within 6 weeks unless otherwise noted
g: Lab work and imaging can be used for both pre-enrollment and pre-treatment evaluation if it the corresponding scheduling restrictions are met.
h:Weekly

*These tests include:

- Complete blood count (CBC), with differential, and platelet count
- Serum Chemistry
- Analysis of blood markers that may be linked with tumor hypoxia
- Needle biopsy of the tumor for study

The experimental portions of the study, meaning those that are outside of standard of care treatment, are the DCA therapy, EF5-PET, the blood draw for secreted marker analysis, and the needle biopsies.

Description of EF5-PET:

In this study, you will undergo special imaging procedures known as PET scans, some of which are experimental. Positron emission tomography (PET) is a type of scan that is based on the administration of a small amount of a radioactive tracer. EF5 is a new and experimental radioactive tracer intended for use with PET scans. Since PET scans do involve administration of radioactive agents, they carry certain medial risks. These risks are discussed in detail below.

PET scans will be performed at up to two time points during this study as outlined above. At each of these time points, a PET scan will be performed using EF5, which accumulates in cells with low oxygen. EF5 is eliminated in the urine.

Each PET scan will be performed as follows: a needle with a small tube will be placed into a vein (IV access), usually in the arm or hand. A standard dose of the radioactive agent, EF5, will then be injected through the IV site. The IV injection might be accompanied by a metallic taste for a few seconds and might evoke a cool sensation near the site of the injection. The scanning procedure is very much like an x-ray CT scan. Approximately 90 to 120 minutes after the injection of the radioactive agent, you will be positioned on the PET scanner table. The acquisition of data for obtaining

images will then begin, and it will be necessary that you remain still for the duration of the scan. Each PET examination will last approximately 30 minutes. Confinement in the PET scanner can cause claustrophobia (anxiety), occurring in about 5% of patients. If you develop this feeling of claustrophobia, you should tell the study doctor or the technologist who is in the room that you cannot continue the study and it will be terminated. You have the option of continuing the study after taking a standard medication to help you relax.

Blood draws and injections are the only invasive procedures performed. The imaging itself is non-invasive. Your samples will be sent to a Stanford laboratory for analysis. Samples left over after analysis may be saved for future research. If you would not like your samples to be saved, you have the option to indicate this, in which case samples will only be kept if needed by your doctor for standard care.

Tissue Sampling for Future Research

Research using tissues is an important way to try to understand human disease. You have been given this information because the investigators want to include your tissues in a research project and because they want to save the samples for future research. There are several things you should know before allowing your tissues to be studied.

Your tissues will be stored in a Stanford University lab and will be de-identified, but linked to your personal health information.

You have the right to refuse to allow your tissues to be studied now or saved for future study. You may withdraw from this study at any time. The investigators might retain the identified samples, e.g., as part of your routine clinical care, but not for additional research.

The results of the study of your samples will be used for research purposes only and you will not be told the results of the tests.

Any tissues you have donated which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, donors of tissues do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

Please initial your choice:

_____ I consent to my samples being saved for future research

_____ I do not consent to my samples being saved for future research

Women of Childbearing Potential

Pregnant women are not eligible for this study. If you are a woman who is able to become pregnant, it is required that you will use an effective 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:

- 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.
- Accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control.
- 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 Protocol Director and study staff.
- Be present on correct dates of imaging examination.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant or gotten your partner pregnant.
- Ask questions as you think of them.

- Tell the Protocol Director or research staff if you change your mind about staying in the study.

While participating in this research study, you should not take part in any other research project without approval from the Protocol Directors of each study. This is to protect you from possible injury arising from such things as extra blood drawing, unnecessary imaging, the possible interaction of research drugs, or other similar hazards.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you withdraw from the study, then you must notify the study protocol director immediately and/or research coordinators.

The Protocol Director 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 Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions. Treatment for cancer can often be difficult to tolerate. There may also be other side effects that we cannot predict. You should feel free to ask questions at any time. Medication will be given to help with symptoms as best as possible.

Risks Associated with DCA chemotherapy:

The common side effects of DCA are:

- Lowering of the white blood cell and red blood cells
- Low platelets with risk of bleeding and decreased ability for clotting
- Fatigue, weight loss
- Loss of appetite
- Nausea, vomiting
- Mouth sores, taste disturbances
- Abnormal blood tests
- Numbness, tingling in hand and foot area

Less likely but serious side effects of chemotherapy:

- Peripheral neuropathy

Very Unlikely side effects of chemotherapy:

- Death

Risks Associated with Blood draws:

There are no foreseeable risks associated with the blood draw except the unlikely event of infection and bruising at the site of collection. Whenever possible, blood draws will coincide with when you are having them for standard care anyway.

Risks Associated with Needle Biopsy:

The risks of the tumor biopsy procedure are mainly pain, bleeding, bruising, and infection. Depending on the location of the tumor, there is a small risk of injury or damage to the nearby organs or tissues. Your doctor may use a local anaesthetic agent or a medicine to calm your nerves before or during the biopsy procedure. Your physician will discuss these comfort measures when he explains the procedure to you.

Although every effort is made to minimize the risks associated with a study procedure, a biopsy could very rarely result in the need for surgery. Surgery may be required, for example, if the needle were to cross a vital structure, like a large blood vessel.

Risks Associated with EF5-PET and FDG-PET/CT:

The EF5-PET procedure may involve risks to the participant, which are detailed below.

No adverse events have been reported for diagnostic EF5 administration at the strength described for this study. Thus no adverse effects are expected as a result of the administration of EF5. The proposed EF5 dose is less than 0.001% of the recommended

safe intravenous dose. EF5 is an investigational agent and has not yet been approved by the FDA.

EF5, FDG and CT will expose you to radiation during this research. Because radiation is part of the test, there is always a small risk that cells or tissue may have received some damage following the PET and PET/CT procedure. However, the radiation levels from the tracer that is sent throughout the body are very low. Your maximum total effective dose for all research procedures involving radiation will be about 3500 millirems. Your dose will be less than this if you have fewer PET scans.

There may be risks to you (or your embryo, fetus, or nursing infant if you become pregnant) that are currently unforeseeable.

In addition, following the scan, you may find that your arm is a little bit sore or that you experience redness where the IV was placed in the arm.

POTENTIAL BENEFITS

The benefit of participating in this study is to learn whether DCA for treating recurrent head and neck cancer offers any effect against with low risk of side effects. We hope that the information learned from this study will help patients with similar situations tobe treated in a safe and effective manner in the future. We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

The alternative is to not participate and receive possible second-line chemotherapy, other experimental research protocols, or best supportive care.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.
If you decide not to participate, tell the Protocol Director. You may still be able to pursue treatment for your disease with more standard therapy and will not lose any benefits to which you would otherwise be entitled.

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.

CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.
The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed**.**

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

One of the purposes of this research study is to obtain data or information on the safety and effectiveness of EF5 as a prognostic imaging tool; the results will be provided to the Food and Drug Administration and other federal and regulatory agencies as required.

Authorization to Use Your Health Information for Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The study will be to determine the maximally tolerated dose of DCA chemotherapy for recurrent head and neck cancer, and efficacy will be measured with EF5-PET and FDG-PET imaging as well as with serum markers. Your health information will be used in screening and in the analysis of data garnered from the study. The data may be used in clinical publication but all patient-specific information will be anonymized.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Daniel Chang, MD, 300 Pasteur Drive, MC 5847, Stanford, CA 94305.

What Personal Information Will Be Used or Disclosed?
Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to your laboratory

results, imaging results, pathology results, medical history, and other data gathered from physician examinations. Individual identifiers including name, date of birth, and medical record number will only be disclosed to necessary personnel at Stanford.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director: Dr. Daniel Chang
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff
- Laboratory Researchers

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- The National Institutes of Health
- Radiation Therapy Oncology Group
- Food and Drug Administration
- National Cancer Institute
- Data Safety Monitoring Board

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will expire December 31, 2108.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a

medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Participant Date

FINANCIAL CONSIDERATIONS

Payment
You will not be paid to participate in this research study.

Costs
If you participate in this study, there may be additional costs involved. These include the personal time it will take to come to all of the study visits.

The study will pay for those services, supplies, procedures, and care associated with this study that are not a part of your routine medical care. If you would like to review the list of such covered services, supplies, procedures and care, please tell us now or at any time during the study.

Participation in this study is not a substitute for health insurance. You and/or your health insurance must pay for those services, supplies, procedures, and care that you require during this study for routine medical care. You will be responsible for any co-payments and/or deductibles as required by your insurance.

Sponsor

The National Institutes of Health is providing some financial support for this study.

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be**

responsible for any associated co-payments or deductibles as required by your insurance.

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

Additionally, Stanford is not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form.

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 Protocol Director, Dr. Daniel Chang. You may contact him now or later at 650-724-3547.

Injury Notification: If you feel you have been hurt by being a part of this study, please contact the Protocol Director, Dr. Daniel Chang at 650-724-3547.

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 (650)-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

Appointment Contact: If you need to change your appointment, please contact Alice Banh at (650) 723-1423.

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.

May we contact you about future studies that may be of interest to you? ☐ Yes ☐ No

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

_____ _____
Signature of Adult Participant Date

_____ _____
Signature of Person Obtaining Consent Date

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature of witness Date
(e.g., staff, translator/interpreter, family member, or other person who speaks both English and the participant's language)

- Translated short form must be signed and dated by both the participant (or their LAR) and the witness.
- The English consent form (summary form) must be signed by the witness and the POC. The non-English speaking participant does not sign the English consent.
- The non-English speaking participant should not sign the HIPAA participant line