Protocol Title:

Pilot Study of the Effect of High Doses of Radiation on Bone Metabolism and Structure in Patients Treated with Adjuvant Radiotherapy and Surgery for Sacral Tumors
[Sponsor Protocol Number: *14-208*]

DF/HCC Principal Research Doctor / Institution:
Joseph H. Schwab, MD / Massachusetts General Hospital

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have been diagnosed with a tumor in your sacrum and surgery and/or radiation are planned as part of your treatment. For the purpose of this research, you will be referred to as a "participant". This research study is evaluating the effects of high energy radiation on bone, with a specific interest in reducing the rate of sacral fractures.

It is expected that about 30 people will take part in this research study.

The National Cancer Institute is supporting this research study by providing funding.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

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B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a pilot study, which is a small study used to see if a full-scale project is practical. This study is designed to characterize the effects of high energy radiation on bone breakdown, with a specific interest in reducing the rate of sacral fractures. Although radiation is very important in managing tumors, it is related to complications such as bone fractures. In this research study, we are looking to determine changes in blood markers, bone density, and bone structure following radiation and to better understand the reason for these changes. We are asking for your consent to take blood samples, bone biopsies, and CT scans for research to help us determine these changes.

The results of this study will hopefully lead to a better understanding of blood markers and other factors that reveal an increased risk of a fracture after radiation. They will also help expand our knowledge about why these changes occur. Ultimately, the results of this study may form the basis for reducing the rate of bone fractures following radiation.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you can choose not to participate. You will still receive treatment as determined by you and your doctor whether you participate in this study or not.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Before the research starts (screening): After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

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- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **A review of your medical records,** to confirm that you are eligible to participate in this study.
- **Blood tests.**
- **Pregnancy test** (if you are a female able to become pregnant), to confirm you are not pregnant.

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

After the screening procedures confirm that you are eligible to participate in the research study: If you take part in this research study, you will have the following procedures, described below. If possible, all of these procedures will be performed on the same day as your regularly scheduled clinic visits. Some visits may last several hours.

- ***Blood tests:*** You will have blood samples drawn at the start of the study and at four additional time points during the study (see the research study plan for details). If possible, these samples will be taken at the same time as the blood draws that are a part of your normal medical care and evaluation so that they will not involve any additional needle-sticks or visits. Some study participants may already have a central venous catheter. If so, we will draw the blood samples from these catheters whenever possible. In the event that a peripheral blood draw is necessary, we will clean the skin with an alcohol wipe, insert a needle into one of the large veins of your arm, and draw blood into tubes for collection. Blood will be analyzed for markers related to bone formation. We will store your blood samples and health information for future research related to effects of high dose radiation on bone. We will label all your samples and health information with a code instead of your name. The key to the code connects your name to your health information and samples. The research doctor will keep the key to the code in a password protected computer/locked file.
- ***Imaging tests:*** We will assess your bone by quantitative CT scan once at the start of the study and at one additional time point during the study. If possible, we will use the information from scans that you have as a part of your normal medical care and evaluation so you do not need to undergo

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an additional scan. The CT scan will be analyzed to determine your bone density.

- ***Study drug diary:*** You will be given a study drug-dosing diary for each treatment cycle. Each treatment cycle lasts 3 days, during which time you will be taking the study drug four times daily. The diary will include special instructions for taking the study drug. The study drug will allow us to see how much the bone has grown from the time you begin taking the first study drug to the time that you stop taking the second study drug.
- ***Bone biopsy:*** If you are undergoing surgery, you will have two bone biopsies during each of your two surgeries. One biopsy during each surgery will be taken from the pelvis and the second from the sacrum. In most cases, the biopsy site will be accessible through the incision made for the surgery. However, in those rare cases when the biopsy site is not accessible via the incision made as part of the standard of care, then a separate small incision (at most 3 cm long) will have to be made. The bone biopsy itself will consist of taking a small sample of bone just under 1/3 of an inch in diameter. Bone biopsies will be evaluated in many ways including for bone strength, bone composition, bone growth, and bone structure. Please know that if the investigator leaves the institution, the research and the tissue might remain at the DF/HCC or might be transferred to another institution. We will store your bone biopsies and health information for future research related to effects of high dose radiation on bone. We will label all your biopsies and health information with a code instead of your name. The key to the code connects your name to your health information and samples. The research doctor will keep the key to the code in a password protected computer/locked file.

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Research Study Plan

Non-Surgical Study Plan:

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Final Visit
Time point	Screening	Start RT Baseline	Halfway RT ~3.5 Weeks	End of RT ~7 Weeks	~3Months after RT	~6 Months after RT	~12Months after RT
Medical History	X						
Blood Test	X	X	X	X	X	X	
CT scan		X			X		
Pregnancy Test	X						

RT = radiotherapy
* Study visit are dependent on treatment events like start/end of pre- or post-op radiotherapy and surgery. Therefore treatment delay will result in delay of study visits.

Surgical Study Plan:

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	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 9	Visit 10	Visit 11	Final Visit
	Before Surgery				Surgery Week		After post-op RT	Follow-Up		
	Screening	Start RT Baseline	End RT ~5.5 Weeks	3-5 days before surgery	Surgery stage 1	Surgery stage 2	End post-op RT	1 month after post-op RT	4 months after post-op RT	10 months after post-op RT
Medical History	X									
Eligibility blood test	X									
CT scan		X		X						
Study Blood test		X	X				X	X	X	
Bone Biopsy					X	X				
Dispense drugs	X		X							
Pregnancy Test	X									

RT = radiotherapy

* Cycle 1 drugs will be taken between visit 1 and 2. Cycle 2 drugs will be taken between visit 3 and 4* Study visit are dependent on treatment events like start/end of pre- or post-op radiotherapy and surgery. Therefore treatment delay will result in delay of study visits.

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this research study for about 1.5 years.

The research doctor may decide to take you off the research study for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens

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- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that there may be side effects from the study drug. These and other risks are detailed below.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Blood Tests:
Blood draws for study blood tests will be combined with blood draws that are a part of your regular medical care whenever possible. Risks associated with blood draws include:

- A small amount of pain.
- The development of a bruise at the blood draw site.
- Rarely, people may faint after a blood draw.
- Rarely, an infection at the blood draw site.
- Rarely, nerve damage at the blood draw site.

Cancer research often includes biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures done only for the purposes of research.

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Radiation Risks Associated with Scans and X-Rays:

While you are in this research study CT scans may be used to evaluate your disease. The frequency of these exams is slightly greater than what you would receive as standard care. In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

Risks Associated with Study Drugs:

Tetracycline and demeclocylcine are commercially available which means that the FDA has approved them for use in patients. They are widely and frequently used throughout the United States. Their risks are described below.

Risks Associated with *Tetracycline*:

Frequent (Between a 10-50% chance that this will happen)

- Tooth discoloration (in young children)

Occasional (Between a 1-10% chance that this will happen)

- Sensitivity to sunlight
- Reduced bone growth (in fetuses)

Rare (Less than a 1% chance that this will happen)

- Itching
- Nausea
- Vomiting
- Abdominal cramps
- Loss of appetite and weight loss
- An abnormal touch sensation, such as burning or prickling
- Diarrhea
- Discoloration of the nails
- Infection
- Incomplete tooth formation (in young children)
- Liver damage
- Kidney damage
- Allergic reaction that may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, it can be severe or life threatening
- Peeling of the skin over large areas of the body
- Increased pressure around the brain

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- Inflammation, irritation or swelling of the esophagus, the tube that leads from the back of the mouth to the stomach
- Inflammation of the colon
- Inflammation of a vein that occurs when a blood clot forms
- High levels of nitrogen-containing compounds in the blood. This is related to poor kidney function
- Inflammation of the small intestine. This could become severe and cause abdominal pain, cramping, dehydration, diarrhea, and fever
- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening
- Inflammation of the sac around the heart. May manifest as chest pain that varies with each breath. Pain often increases when lying down and decreases upon sitting up. Fever, cough, and palpitations are common as well. This may be serious and require medical intervention
- Kidney failure which is when both of your kidneys fail and your body holds fluid which can be serious or life threatening. Your blood pressure rises and harmful wastes build up in your body. You may experience fatigue, nausea, and loss of appetite. When this happens, you need treatment to replace the work of your failed kidneys such as dialysis

Risks Associated with *Demeclocycline*:

Frequent (Between a 10-50% chance that this will happen)

- Tooth discoloration (in young children)

Occasional (Between a 1-10% chance that this will happen)

- Sensitivity to sunlight
- Reduced bone growth (in fetuses)

Rare (Less than a 1% chance that this will happen)

- Nausea
- Vomiting
- Loss of appetite and weight loss
- Ringing in the ears
- Dizziness
- Headache

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- Rash
- Diarrhea
- Darkening of the skin
- Small points of discoloration of the neck (after prolonged periods of taking the medication)
- Tooth discoloration (in adults)
- Inflammation of the tongue
- Difficulty swallowing
- Visual disturbances
- Throat ulcers
- Joint pain
- Achiness in the joints accompanied by a facial rash
- Infection
- Fungal infection
- Serious allergic reaction
- A specific type of allergic reaction typically involving a single patch on the skin
- Increased pressure around the brain
- Involuntary movements of the arms and legs
- Thyroid dysfunction
- Swollen raised areas on the skin that are intensely itchy
- A disorder in which a defect in the kidneys causes a person to pass a large amount of urine
- Accumulation of a substance, such as pus or protein, in the lung
- A condition in which the number of eosinophils (a type of white blood cell) in the blood is greatly increased. Eosinophilia is often a response to infection or allergens (substances that cause an allergic response)
- A condition in which there is a lower-than-normal number of neutrophils (a type of white blood cell)
- Low number of platelets, which may cause bleeding and bruising. Bleeding may be serious or life threatening and may required a blood transfusion
- Destruction of red blood cells that leads to anemia
- Swelling that happens just below the surface of the skin, most often around the lips and eyes. When you have an allergic reaction, your body produces histamine, which causes blood vessels to swell. Angioedema is a deeper swelling
- Whole-body inflammation from a hypersensitivity reaction

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- Inflammation of the liver
- Inflammation of the small intestine and colon
- Inflammation of male genitalia
- Blood vessel inflammation causing skin rash, abdominal pain, and joint arthritis
- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening
- Inflammation of the sac around the heart. May manifest as chest pain that varies with each breath. Pain often increases when lying down and decreases upon sitting up. Fever, cough, and palpitations are common as well. This may be serious and require medical intervention
- Severe skin and gut lining reaction that may include rash and sloughing or death of tissue. This may manifest as various blisters, hives, and other lesions in various locations on the body including palms and soles, face & other extremities. This is serious and may be life threatening
- Kidney failure which is when both of your kidneys fail and your body holds fluid which can be serious or life threatening. Your blood pressure rises and harmful wastes build up in your body. You may experience fatigue, nausea, and loss of appetite. When this happens, you need treatment to replace the work of your failed kidneys such as dialysis
- Peeling of the skin over large areas of the body
- A severe disorder in which your skin and mucous membranes react severely to medication
- Liver damage
- Liver failure

Reproductive Risks:
The drugs used in this research study may affect a fetus. Until after the second study CT scan, you should not become pregnant or father a baby, and should not nurse a baby. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child. We can provide counseling about preventing pregnancy for either male or female study participants.

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Risks Associated with Biopsies:
Biopsies are normally performed under the guidance of an imaging technique. The risks may include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.
- Rarely, an infection at the biopsy site.

Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

This study will not directly benefit you. Taking part in this research study may help us learn more about how radiation affects bone, specifically in the sacrum. We hope that the information learned from this research study will help identify those patients who are at risk of a fracture and provide the basis for preventative treatments in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

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I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for your participation in this research study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You will not be charged for the study drugs tetracycline and demeclocycline.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services is:

- Massachusetts General Hospital: (617) 726-2191

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

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K. WHAT HAPPENS IF I AM INJURED OR SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for Massachusetts General Hospital (MGH) to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

We will label all your blood and bone samples and health information with a code instead of your name. The key to the code connects your name to your health information and samples. The research doctor will keep the key to the code in a password protected computer/locked file.

The results of this research study may be published. You will not be identified in publications without your permission.

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.

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M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Massachusetts General Hospital (MGH)

- Joseph Schwab, MD: (617) 643-2483
- Quirina Thio, Research Fellow: (857) 200-7487

qthio@mgh.harvard.edu
24-hour contact: If an urgent issues arises outside of normal business hours, please contact Joseph Schwab, MD, at (617) 543-5227

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

N. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;

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- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug for the purpose of this or other research relating the study drug and its use in cancer; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, and its agent(s): The National Cancer Institute
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or

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necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"

O. OPTIONAL RESEARCH STUDIES:

You are being asked to participate in some optional studies. If you decide not to participate in any of the optional studies, you can still participate in the main

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research study. Please take your time to make your decision and discuss it with others and your primary care physician.

Your participation in these optional research studies is voluntary, and you will not be penalized or lose any benefits if you refuse to participate or decide to stop.

Optional Study #1:

The biopsies that will be taken during the two stages of your surgery are of great value and contain a lot of information. We will be preforming a set of measurement on the biopsies that will give us a great amount of information. Even though, there still is a lot of information that we are not collecting in this study. This could be because our current budget does not allow it, or because techniques of retrieving this information are not yet available. We therefore want to store you bone biopsies for future research related to the effects of high dose radiation on bone.

Please indicate whether or not you want to take part in the optional research studies.

☐ Not applicable

☐ Yes _____Initials _____Date

☐ No _____ Initials _____Date

Optional Study #2:

The blood samples that will be taken during this study are of great value and contain a lot of information. We will be preforming a set laboratory test that will give us a great amount of information. Even though, there still is a lot of information that we are not collecting in this study. This could be because our current budget does not allow it, or because techniques of retrieving this information are not yet available. We therefore want to store your blood samples for future research related to the effects of high dose radiation on bone.

Please indicate whether or not you want to take part in the optional research studies.

☐ Not applicable

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☐ Yes _____Initials _____Date

☐ No _____ Initials _____Date

P. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

_____ _____

Signature of Participant Date
or Legally Authorized Representative

_____

Relationship of Legally Authorized Representative to Participant

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Adult Participants

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is illiterate

The consent form was read to the participant who was given the opportunity to ask questions.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

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