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Official Title: A Pilot Study Analyzing Preoperative Stereotactic Radiosurgery (SRS) With Gamma Knife (GK) for Brain Metastases
Date: September 19, 2023

EFFECTIVE

September 19, 2023

MCW IRB

Medical College of Wisconsin
INTRODUCTION TO THE INFORMED CONSENT

IIT-BOVI-GK-BRAIN-METASTASES: A Pilot Study Analyzing Preoperative Stereotactic Radiosurgery (SRS) with Gamma Knife® (GK) Icon™ for Brain Metastases

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Definitions

Stereotactic radiosurgery – a non-surgical radiation therapy used to treat small tumors of the brain. This treatment uses focused beams of radiation to target tumors in the brain while leaving surrounding healthy tissue unaffected

Performance status – an assessment of your overall health and ability to perform daily tasks

Neurocognitive Tests: You will also be asked to complete a brief series of tests to evaluate your thinking abilities such as memory and verbal skills, with a series of mental function tasks given by an examiner. Researchers will use this information to understand how your treatment and illness affects your mental function.

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Purpose

This project is being done to test if a new approach of using stereotactic radiosurgery to treat your brain tumor(s) followed by surgery to remove it (them) will result in better outcomes compared to traditional treatment plans.

Length

- You will be in this research project for about 20 months, including follow-up visits.

Procedures

All subjects in this study will have stereotactic radiosurgery followed by surgical resection to remove their tumors.

List of visits:

- Screening Visit(s)
  - Total Number: 1
  - Total Time: approx. 4-8 hours
- Treatment Visits
  - Total Number: 2
  - Total Time: approx. 6-10 hours
- Post-Surgical Resection Visit(s)
  - Total Number: approx. 1-2
  - Total Time: approx. 4-6 hours
- Follow-up Visits (every 3 months)
  - Total Number: approx. 6-12
  - Total Time: approx. 3-4 hours each

Procedures that will occur at various visits:

Invasive Procedures

- Surgical resection of your brain tumor(s)
- Blood collection for pregnancy test, if applicable (a urine test may also be done)

Non-invasive Procedures

- Physical exam
- Stereotactic radiosurgery
- Performance status
- Neurocognitive testing
- Quality of Life questionnaires
- MRI scans

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

Stereotactic Radiosurgery risks:

- Temporary (short-term) pain from with the head frame placement (if a head frame is used)
- Headache
- Localized hair loss which may be permanent
- Nausea
- Vomiting
- Allergic reaction to the local anesthesia (rash, itching, nausea, or difficulty breathing)
- Bleeding and/or infection around the head frame (if a head frame is used)
- Swelling of the brain in the treated area which may require treatment with steroids
- Severe local damage to or death of normal brain tissue, which may require surgery to remove

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Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:

- Joining a different project
- Routine care for this condition
- Getting no treatment for this condition

If you have more questions about this project at any time, you can call Michael Straza, MD at 414-805-6700.

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are being invited to participate in this research because you have cancer that has been confirmed to have metastasized (spread) to the brain. You have up to four brain metastases.

A total of about up to 15 people are expected to participate in this research at the Medical College of Wisconsin/Froedtert Hospital.

The Director of the project is Michael Straza, MD in the Department of Radiation Oncology. A research team works with Dr. Straza. You can ask who these people are.

Philanthropic (donations) from the Medical College of Wisconsin are funding this research project.

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you do not agree to join, or if you leave, you will not be penalized or lose any benefits that you had before starting the research project. Even if you join this project, you do not have to stay in it. You may stop at any time. Take as much time as you need to make your choice.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

Traditional treatment plans for tumors that have metastasized to the brain include different regimens of radiation alone, surgery alone, a combination of radiation before surgery, or a combination of surgery followed by radiation. Researchers are looking for novel treatment plans that result in longer survival, reduced rate of cancer recurrence, and fewer cognitive (brain function) side effects. The purpose of this study is to test if changing the timing of the use stereotactic radiosurgery to treat your brain tumor(s) prior to surgery rather than after surgery to remove it (them), will result in better outcomes compared to previously tested treatment plans.

Your condition may get better, but it could stay the same or even get worse. We hope the information from this study will help us develop a better treatment for cancer patients with brain metastases in the future.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

Study Treatment

All subjects in this study will have stereotactic radiosurgery followed by surgical resection to remove their tumors. Stereotactic radiosurgery uses focused beams of radiation to target tumors in the brain while leaving surrounding healthy tissue unaffected. The specific technique of stereotactic radiosurgery in this study will be Gamma Knife, which is able to take MRI images at the same time as delivering radiation therapy.

Stereotactic radiosurgery is non-invasive. If you participate, you will be sedated so that you do not feel anything. You will lie flat on a table with your head immobilized during the treatment. Your study doctors first will perform an MRI or CT scan of your head to see the size and location of your brain tumors. Then, the stereotactic radiosurgery will be performed over a few hours. You will be able to leave the clinic the same day as receiving your treatment.

Study Visits

The study is divided into 4 periods: Screening, Treatment, Post-Surgical Resection, and Follow-up.

Screening
After you sign the informed consent form, you will visit the clinic to see if you are eligible to participate in the study. The study team will ask you some questions about your health and medications you are taking, perform a physical exam, and run some tests to determine if you are eligible. If some of the tests were completed recently, they may not have to be repeated for the study. The Screening period may last up to 30 days, but treatment must start within 14 days of study enrollment.

Treatment
The Treatment period will consist of receiving stereotactic radiosurgery followed by surgical resection of your tumor(s).

Post-Surgical Resection
You will return to the clinic again one month after your surgical resection. The study team will perform some tests to assess how you are responding to the treatment.

Follow-up
You will then return to the clinic, every 3 months, at 3, 6, 9, 12, 15, and 18 months after your Surgical Resection visit. The study team will continue to monitor your health over time. Your cancer will be imaged by MRI scans as determined by your doctor. You will also complete questionnaires and other assessments to evaluate your neurocognitive health and overall quality of life.

Study Assessments

Screening
You will need to have all or some of the following exams, tests, or procedures to find out if you can be in the study. They may be done even if you do not join the study. If some of the tests were completed recently, they may not have to be repeated.

- Informed consent: Prior to any study-related procedures being performed, you will be required to voluntarily sign and date this consent form.
- Adverse events: You will be asked about if you experienced any changes in your health
- Medications: You will be asked about any changes in your current medications, including over-the-counter medications, vitamins, and herbal supplements
- Physical examination: You will receive a complete physical examination, including weight and height.

- Vital signs: Your blood pressure, temperature, and heart rate will be checked.
- Medical history: You will be asked about your health status, including previous treatments for your cancer
- Performance status: An assessment of your overall health and ability to perform daily tasks
- Blood or urine tests: A blood or urine sample will be collected for pregnancy, if you are a female patient capable of having children
- Neurocognitive assessments: A series of tests to evaluate your thinking abilities such as memory and verbal skills
- Quality of Life questionnaires: Questions about daily activities and mental, physical and emotional symptoms, etc.
- MRI: You will have a brain MRI to assess the size and location of your brain tumor(s)

Treatment

Your study doctor or a member of the study team will let you know if you are eligible to participate in the study. If you are unable to participate in the study, the study doctor will discuss other treatment options with you.

You will have stereotactic radiosurgery treatment followed by surgical resection of your tumors within 1-10 days. On both days, the following additional assessments will also be performed:

- Adverse events: You will be asked about if you experienced any changes in your health
- Medications: You will be asked about any changes in your current medications, including over-the-counter medications, vitamins, and herbal supplements

Post-Surgical Resection

A month after surgical resection, you will return to the clinic to evaluate your health. The following assessments will be performed at this visit:

- Adverse events: You will be asked about if you experienced any changes in your health
- Medications: You will be asked about any changes in your current medications, including over-the-counter medications, vitamins, and herbal supplements
- Physical examination: You will receive a complete physical examination.
- Vital signs: Your blood pressure, temperature, and heart rate will be checked.
- Performance status: An assessment of your overall health and ability to perform daily tasks
- Quality of Life questionnaires: Questions about daily activities and mental, physical and emotional symptoms, etc.
- MRI: You will have a brain MRI to assess the size and location of your brain tumor(s)

Follow-up

You will then return to the clinic, every 3 months, at 3, 6, 9, 12, 15, and 18 months from your Post-Surgical Resection visit for further evaluation of your health. The following assessments will be performed at these visits:

- Medications: You will be asked about any changes in your current medications, including over-the-counter medications, vitamins, and herbal supplements
- Physical examination: You will receive a complete physical examination.
- Vital signs: Your blood pressure, temperature, and heart rate will be checked.
- Performance status: An assessment of your overall health and ability to perform daily tasks
- Neurocognitive assessments: The tests performed at screening will be repeated every 6 months during follow-up
- Quality of Life questionnaires: Questions about daily activities and mental, physical and emotional symptoms, etc.
- MRI: You will have a brain MRI to assess the size and location of your brain tumor(s)

B2. HOW LONG WILL I BE IN THE PROJECT?

You will be in this research project for about 20 months, including follow-up visits.

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.

The research doctor can tell you about the effects of stopping, and you and the research doctor can talk about what follow-up care would help you the most.

You might be asked to come back for one more visit to check your health.

The research doctor may take you out of this project at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

B4. ARE THERE ANY SPECIAL INSTRUCTIONS WHILE I AM IN THE PROJECT?

You should tell the study doctor of any changes in your health during the study.

You should tell the study doctor of any changes in your current medications, including over-the-counter medications, vitamins, and herbal supplements.

You should not breastfeed a baby while in this study.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that you may get an intervention that does not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from the intervention itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems, side effects, or changes in your health.** In an emergency, call 911.

C2. RISKS OF STEREOTACTIC RADIOSURGERY (SRS) AND SURGICAL RESECTION

The research intervention itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away.

Possible Side Effects of Stereotactic Radiosurgery (SRS)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving SRS, more than 20 and up to 100 may have:

- Temporary (short-term) pain from with the head frame placement (if a head frame is used)

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving SRS, from 4 to 20 may have:

- Headache
- Localized hair loss which may be permanent
- Nausea
- Vomiting
- Allergic reaction to the local anesthesia (rash, itching, nausea, or difficulty breathing)
- Bleeding and/or infection around the head frame (if a head frame is used)
- Swelling of the brain in the treated area which may require treatment with steroids
- Severe local damage to or death of normal brain tissue, which may require surgery to remove

RARE, AND SERIOUS

In 100 people receiving SRS, 3 or fewer may have:

- Decreased brain function such as motor function (coordination/movement)
- Hardening of the arteries in the brain which rarely may lead to strokes many years after stereotactic radiosurgery
- A second new cancer caused by radiation, in the brain or nearby organs which rarely may occur many years after stereotactic radiosurgery
- Damage to vision tracts (eye damage) with the possibility of permanent blindness

Long term effects of the radiation or radiosurgery used in this study include an increased risk of developing other cancers.

Possible risks of Surgical Resection

COMMON, SOME MAY BE SERIOUS

In 100 people receiving neurosurgery 20 to up to 90 patients may have:

- Pain
- Headache
- Nausea
- Vomiting

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving neurosurgery, 15 to up to 20 patients may have

- Bleeding
- Infection

RARE AND SERIOUS

In 100 people receiving neurosurgery, less than 5 patients may have

- Stroke
- Permanent brain injury (i.e., arms and legs not functioning properly, issues with speech)
- Complications from anesthesia (i.e., problems with your heart or lungs)

C3. OTHER RISKS OF THIS RESEARCH PROJECT

Other procedures that are part of the research also involve some risks:

Blood collection (if a blood sample needs to be collected for a pregnancy test)
Blood collection may cause some discomfort, bleeding, or bruising at the puncture site. A small blood crust or swelling may occur at this site. In rare cases, fainting or local infection may occur. If you feel discomfort during blood collection, please report this to the study doctor or staff at the time.

Magnetic Resonance Imaging (MRI Scan)
MRI, which uses a large magnet instead of x-rays to take pictures of your body, you may feel mild vibrations throughout your body. The machine will produce a loud knocking noise. This is normal. You will be given earplugs to protect your ears. Some people, especially those who tend to feel uncomfortable in small or closed spaces, may feel “closed in” and become anxious while in the scanner. The scanner has an intercom, which will allow you to speak to the staff during the procedure. If you feel ill or anxious during scanning, tell the MRI staff and the scanning will be stopped if you wish.

The MRI will require a catheter to be inserted into one of your veins in order to inject the MRI contrast agent. This may cause skin irritation, bleeding, and/or infection. You may have an allergic reaction to the contrast agent.

The magnetic field used in MRI scanning may harm people who have metal in their bodies (pacemakers, neurostimulators, certain clips, or staples from surgery). It may cause problems with devices, such as pacemakers. If you have metal in your body or a pacemaker, you should not have an MRI. Your study doctor will discuss with you whether you should have a MRI scan with a contrast agent based on your health status.

Neurocognitive Testing and Questionnaires
The answers that you give are confidential, but there is always a risk that your answers will be read by people who should not read your personal information. You may also feel uncomfortable completing some of the assessments.

Privacy and Confidentiality
Another risk may be loss of confidentiality. Every effort will be made to keep your research records confidential but we cannot guarantee it. Depending on the kind of information being collected, if your research information were accidentally seen, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the project director about whether this could apply to you.

C4. REPRODUCTIVE RISKS

Risks to subjects who could become pregnant
We do not know if the intervention causes harm to a baby, so we do not want anyone who might be pregnant to enter the project.

You should not become pregnant or nurse a baby while in this project. You must tell the research doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the project.

Risks to a subject's partner(s)
If you and your partner(s) are able to become pregnant, one or both of you must use some form of effective birth control, because it is unknown if intervention could affect a baby. You must tell the research doctor right away if you think your partner is pregnant.

Birth control methods for all subjects
Check with the research doctor about the birth control methods needed for this project and how long to use them. Some methods might not be good enough for this project. If you are having sex that could lead to pregnancy, you should use one form of highly effective birth control while you are in this project.

This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally, unless directed otherwise if you have breast cancer
- Having birth control shots or patches such as Depo-Provera, unless directed otherwise if you have breast cancer
- Surgical sterilization (hysterectomy/tubal ligation or vasectomy)

- Limiting sexual activity to a partner who has undergone surgical sterilization
- Use of an intrauterine device (IUD), unless directed otherwise if you have breast cancer
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam (Female and male condoms should not be used together)
- Use of diaphragm with condoms ("double barrier")

You should continue using birth control for 4 months after stopping the study intervention.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

We don't know if this study will help you. Your condition may get better, but it could stay the same or even get worse. We hope the information from this study will help us develop better treatment plans for cancer patients with brain metastases.

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

Most of the medical care that you will receive in this project is considered routine care for your condition and would be recommended whether or not you join the project. Costs for routine care will be billed to you or your insurance carrier. For routine clinical care, you will be responsible for paying any copayment, coinsurance, or deductible that is required by your insurance carrier.

Activities / costs that are part of the project will not be billed to you or your insurance company. These are:

- Neurocognitive testing and Quality of Life questionnaires

Some insurers will not pay for drugs, tests or hospitalization that are part of research, so check with your insurer before you join this project. If you have questions regarding costs, please contact Dr. Straza.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

There is no payment for being in this project.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.

Your other choices may include:

- Routine care for this condition
- Surgery alone, whole brain radiation therapy (WBRT) alone, WBRT followed by surgery, surgery followed by WBRT, and surgery followed by SRS
- Joining a different research project

The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information about the intervention that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries directly related to your participation in this research project will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctors right away. Contact information: Michael Straza, MD, 414-805-6700

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

- If you have more questions about this project at any time, you can call Michael Straza, MD at 414-805-6700.
- If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this project?

To be in this research project, the research team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the project. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); Versiti, Inc.; Children's Hospital of Wisconsin (CHW); any Froedtert Health Affiliate- Froedtert Hospital (FH), Inc.; Froedtert Menomonee Falls Hospital; Froedtert West Bend Hospital; Froedtert & The Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:

- Past and present medical records to document relevant pre-existing conditions
- Records about your study visits and results of tests done during the study
- Records about phone calls made as part of this research
- Research records

E2. Who will see the health information collected for this project?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

The research team may share your information with people who don't work at MCW/Froedtert Hospital because they planned, pay for, or work with us on this project. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this project, we plan to share information with those doctors, researchers or government representatives working with us on this project at the institutions or companies listed here:

- Government agencies in the U.S., such as the Food and Drug Administration (FDA), National Cancer Institute (NCI), and National Institutes of Health (NIH);
- Other federal and state agencies, such as the Office of Human Research Protections, (OHRP);
- Others required by law
- Florence Healthcare, Inc.

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all project records.

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information and/or biospecimens, the information and/or biospecimens may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. If you have questions, you can talk to the research doctor about whether this could apply to you.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to Michael Straza, MD at

Department of Radiation Oncology
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee WI 53226

The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we will decide that you cannot continue to be part of the project. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE PROJECT

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.

You can look up this project by referring to the ClinicalTrials.gov number (NCT04545814) or by asking the research team for a printed copy.

CONSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Witness, if applicable *please print*	**Signature of Witness**	**Date**
Rationale for Use of Witness ☐ Subject has limited/no literacy ☐ Subject has limited English proficiency ☐ Subject has limited/no vision	☐ Sponsor requirement ☐ Other _____	
*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the research team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. The Principal Investigator is responsible and accountable for the research project.*