Consent and Authorization Document

Phase I Study of Stereotactic Radiosurgery Dose Escalation for Brain Metastases

BACKGROUND

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask the research doctor or staff if there is anything that is not clear or if you would like more information. Take time to decide whether or not to volunteer to take part in this research study.

This study is being carried out by the Department of Radiation Oncology & the Department of Neurosurgery at the Huntsman Cancer Hospital at the University of Utah. You are being invited to participate in this study because it is suspected that cancer from another primary disease site has spread to your brain. Tumors that have spread are called "metastases". The brain metastases have been detected by a magnetic resonance image (MRI) or computed tomography (CT) scan and your doctors have recommended that you have stereotactic radiosurgery (SRS) to treat these tumors. SRS is a standard focused radiation treatment that controls these tumors with a noninvasive approach. The purpose of this study is to determine the maximum tolerated dose of radiation received during SRS in patients with brain metastases who have never received radiation to the brain before. There has not been a study of this nature performed, and therefore there is not a consensus among radiation oncologists as to what is the highest dose that brain metastases can receive the first time they are being treated with radiosurgery. The amount of radiation given will depend on the size of the tumor being treated; with smaller tumors receiving more dose overall than larger tumors. Smaller tumors are able to tolerate higher doses given less volume will be irradiated. For example at our institution, small tumors typically receive 24 Gy of radiation, medium tumors receive 18 Gy, and large tumors receive 15 Gy. These doses can vary depending on the institution you are receiving treatment at. In this study, we will increase the dose of radiation to each group by 2 Gy to see if it is tolerated and if we can increase the dose even more to improve control of the metastases. This is a Phase 1 study, which means it is an early human study done on a small number of people to find out about safe dose ranges. We hope that increasing the dose of radiation delivered during SRS will result in improved outcomes and control of these brain tumors.

In this study, up to 117 patients will be enrolled who are diagnosed with metastatic malignancy to the brain, no matter the primary tumor.

STUDY PROCEDURES

Screening

Before you enroll to the study you will sign this informed consent form. You will have a physical exam including a review of your neurological history. You will also be required to take a pregnancy test if you are a woman of child bearing potential.

Pretreatment Imaging

MRI

After you enroll in the study, standard of care pretreatment imaging will be obtained. This includes a MRI scan with administration of the contrast agent gadolinium. The gadolinium is given by intravenous injection and used routinely for most MRI scans. The contrast makes the tumor more visible on the MRI and aids in radiation treatment planning. You will be asked to fill out a standard MRI Patient History & Safety screening questionnaire prior to the MRI that will take less than 5 minutes to complete. If you have questions about this form, please ask the MRI technician. Prior to the MRI, you will be asked to remove all objects that may contain metal from your person including eyeglasses, shoes, jewelry, body piercings, hairpins, barrettes, hair accessories, brassieres with wire supports, clothing with metal snaps, zippers, buttons, pins, any metal objects in your pockets such as coins, knives, clippers, writing implements, cellular phones and other electronic devices. The strong magnetic field in the MRI machine can erase magnetic strips on credit cards and ID cards, so you will be asked to leave your wallet in a safe place and a locker will be provided for you. Please do not wear mascara or eye shadow, or remove them before the scan, as these cosmetics may contain iron particles that could damage your eyes while in the scanner.

The MRI magnet bore is a long cylinder about two feet in diameter and is open at both ends, is well lit, ventilated, and equipped with an intercom so you can remain in contact with the MRI technologists. The relatively confined space within the MRI can cause discomfort for people who fear small enclosed spaces or suffer from claustrophobia. If you experience feelings of discomfort or pain in enclosed spaces or know that you suffer from claustrophobia, please discuss these issues with the study coordinator prior to proceeding. If you find the scan difficult, the technician may provide you with a mild sedative to help you relax. You should not drive after receiving sedation. The MRI system generates loud knocking noises during operation, and you will be provided earplugs to wear. It is vitally important that you be able to remain still for periods of 10-15 minutes during the MRI scan. If you have a condition that might prevent this or are uncertain of your ability to do so, please discuss this with the study coordinator.

Simulation Appointment with CT

The next step is the Simulation appointment, in the Radiation Oncology department. This appointment lasts approximately 1 hour, which will be scheduled after your first consultation appointment with your doctor. The Simulation appointment involves constructing a plastic mask that fits over your head and face, which immobilizes your head so that the position of your head at the time of Simulation remains exactly the same when you come back to receive SRS treatment. The precision and accuracy of the treatment is of upmost importance, and the immobilization and plastic mask allow us to be as accurate as possible. The mask is warmed in a water bath and becomes pliable, at which point it is placed over your face and upper neck by the radiation therapists. The mask has eye holes and nose holes so you can see and breathe with ease and talk to the therapists if necessary. Patients who suffer from claustrophobia may have difficulty with the mask, so please discuss with the study coordinator if you suffer from claustrophobia or have difficulty with confined spaces prior to your Simulation appointment. The Simulation room is a large, open room, and the space is not confined like the MRI machine. You will have to leave the mask on for approximately 15-20 minutes in order to allow the mask to mold to your face as it cools and hardens. Once the mask is properly positioned and the radiation therapists are confident it will hold its shape, a CT

scan of the head is obtained with the mask on. This CT scan does not require intravenous gadolinium contrast and takes less than 1 minute to complete, and then the mask will be removed. The CT scan is a standard of care procedure, and necessary for radiation treatment planning and is used along with the MRI. After the Simulation appointment is completed, you will be given an appointment to return for SRS treatment.

Stereotactic Radiosurgery Treatment

On the day of SRS treatment, you will return to the Radiation Oncology department, there are no restrictions on oral intake or activities prior to this appointment. If you are not on an oral steroid medication, you will be given a single dose of oral steroids by our nurses prior to the treatment. You will then be brought back to the SRS treatment room by the radiation therapists, and will lie on a hard flat table, similar to the table in the Simulation room. Your plastic mask will be placed over your head and you will be aligned in the room by the radiation therapists. X-rays will be taken of your skull in the mask, and your alignment is checked by the radiation therapists, medical physicists, and treating radiation oncologist to ensure that the positioning is perfect. These X-rays are standard of care for alignment purposes. There are video cameras and intercoms in the treatment room so that you are in communication with the radiation therapist at all times. Once it is confirmed you are perfectly aligned, the treatment is delivered. A large machine, called a linear accelerator, moves around you in the room to deliver the radiation. The total treatment time takes approximately 15-20 minutes per tumor; therefore the total time is longer if more than one tumor is treated. You will not feel or see anything during the treatment, and you will not notice the difference between tumors treated with standard doses compared to those treated with the slightly higher doses on-protocol. Once the treatment is completed, your mask will be removed and the radiation therapists will help you down from the treatment table and you will be allowed to go home shortly thereafter.

Procedures after Treatment

You will return home the day of treatment, and one of the study staff will call you within 2-4 days after treatment to see how you are doing or answer any questions you may have. You will return to the Neuro-oncology clinic approximately 4-6 weeks after treatment, and again 12-16 weeks post treatment for follow-up appointments. Prior to these appointments, you will have another MRI scan with gadolinium contrast so that we can evaluate the tumor response to treatment. The clinic visit will entail a physical and neurologic examination, vital signs, and review of your imaging.

After the 12-16 week follow up appointment you will be seen approximately every 2-3 months the first year, 4-6 months the second year and 6-12 months the third year. These visits will include MRI scans, physical and neurologic examination, and review of your imaging.

If at any point you have new symptoms or the tumor starts to grow, or there are new tumors, you will be evaluated by the Neuro-oncology team and a discussion of further treatment, either surgery or radiation, will be had. We will continue to follow your progress as long as you require treatment for the tumor for up to 3 years.

The x-rays, MRI scans, and CT scans done during your participation in this study are considered part of your routine cancer care. You would have this imaging even if you were not participating in this study.

RISKS

Risks from Preoperative Imaging

Magnetic resonance imaging (MRI) uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. If there is metal in your body, such as a cardiac pacemaker, certain types of cerebral aneurysm clips, ferromagnetic foreign bodies, and depending on the location, you will not undergo the MRI. If there is metal in a muscle, for example from a bullet, you experience heating of the metal. If you experience discomfort, the MRI can be discontinued. About 2% of people how are scanned experience feelings of claustrophobia; if this occurs, we can give you a mild sedative to reduce your anxiety.

The contrast agent, gadolinium, which you will be given at the time of the MRI scan, is routinely used in this procedure. A very small number of people develop short-lasting reactions during or just after the drug is injected; including nausea, headache, hot flushes, dizziness and irregular heart beat in 1-2% of patients. These symptoms usually go away by themselves within a few minutes. Occasionally, patients will experience pain and/or swelling at the site of injection for a few days after imaging. A small number of patients develop an allergic reaction to the contrast agent which could include a rash or breathing problems. In extremely rare cases, the heart may stop beating and death may occur. You will be closely monitored and if an allergic reaction develops, you will promptly treated with drugs and helped with breathing if necessary.

Because the possible effects of the strong magnetic fields in the MRI machine and of gadolinium contrast agents on the development of fetuses are unknown, if you are of childbearing age and suspect you might be pregnant, please inform the study coordinator immediately and discontinue your participation in the study for the duration of your pregnancy. If you are of childbearing age and more than 10 days has passes since your last menstrual period you will be asked to take a pregnancy test prior to the MRI. The gadolinium contrast agent may be excreted in minute quantities in the breast milk of lactating women. Because the effects of ingesting this drug on infants are unknown, you should not breastfeed for 36 hours after your MRI scan, but should pump and discard the milk during this period.

Risks from Radiosurgery

You may experience side effects after SRS treatment, most of the side effects are listed below, but there may be other side effects that we cannot predict as side effects vary between patients. Everyone taking part in the study will be carefully watched for any side effects; however doctors do not know all of the side effects that are possible. These side effects can be mild or serious, your health care team may give you medications to help lessen some of these side effects if they present. Many side effects go away quickly within weeks of therapy, but in some cases they can be more serious, long-lasting, or may never fully go away. You should talk to your doctor about any side effects you experience after treatment. You may be at slightly higher risk of experiencing these side effects given that your tumor (or one of your

tumors) will be treated with a slightly higher dose than normal, which may increase the chance you could experience side effects from the treatment.

Likely side effects include mild fatigue the day or two following treatment. Less likely side effects include headache, nausea, vomiting, seizure, pain, swelling of the brain, or hair loss. Rare but serious side effects can include bleeding from the tumor that could cause a stroke or stroke-like symptoms, seizure, swelling of the brain tissue with symptoms not relieved from oral steroid treatment and requiring a surgery to remove the tumor causing swelling. Another rare but serious side effect can include radiation induced death of normal brain tissue which might require a surgery to remove that tissue. A extremely rare but possible side effect is death due to progression of brain tumors, bleeding from brain tumors, or other unforeseeable complications. Again, the risk of these side effects may be slightly more likely given that your tumor (or one of your tumors) will be treated with a slightly higher dose of radiation.

REPRODUCTIVE RISKS

It is possible that if the treatment is given to a pregnant woman it will harm the unborn child. Pregnant women must not take part in this study, nor should women who plan to become pregnant prior to the planned SRS treatment. Women who are at risk of pregnancy will be asked to have a pregnancy test before taking part to exclude the possibility of pregnancy. If you are a sexually active and possibly fertile man or woman, you will be asked to use a medically effective contraceptive during the period prior to SRS treatment and for 3 months after radiation. Acceptable methods of birth control include condoms, oral contraceptive pills, diaphragm, IUD, or the combination. If you become pregnant prior to receiving radiation, you must immediately tell your research doctor. Options will be discussed with you at that time. Whether or not you remain on the study, we will follow the outcome of your pregnancy and we will continue to follow you according to the study plan.

LOSS OF CONFIDENTIALITY

There is a potential risk of the loss of confidentiality for patients involved in this study, although it is a low risk and one that will be mitigated with de-identification of patient health information and with keeping data information on patients enrolled in a safe and secure environment.

BENEFITS

We cannot promise any benefits to you from your being in the study. However, possible benefits may include improved control of the treated brain tumors. Although there may be no direct benefits to you from taking part in this study, the information we get from this study may help us treat futures patients with metastatic brain tumors. We hope that this study will help you, however, this cannot be guaranteed.

ALTERNATIVE PROCEDURES

You may choose not to be in this study. If you do not want to take part in the study, there are other choices, such as proceeding with standard dose SRS treatment, without increasing the dose of radiation if you participate on the study. You may discuss these options with your doctor.

PERSON TO CONTACT

If you have questions, complaints or concerns about this study, you can contact Dr. Dennis Shrieve at 801-581-2396. If you think you may have been injured from being in this study, please call Dr. Shrieve at 801-581-2396. Dr. Shrieve can be reached at this number during regular business hours; Monday through Friday from 8:00 AM to 5:00 PM. At all other times, please call the University of Utah Hospital operator at 801-581-2121 or the Huntsman Cancer Hospital at 801-587-7000 and ask for the Radiation Oncologist on call.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY

If you are injured from being in this study, medical care is available to you at the University of Utah as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance), to the study sponsor or other third party (if applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If you are injured in this study, and want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION

Participation in research studies is voluntary, and they include only people who choose to take part. You may choose to take part in this study or not, and if you decide to participate you can choose to stop at any point in time. No matter your decision, there will be no penalty to your medical care and you will not lose any of your regular benefits. We will still give you medical care and answer any questions you have. Your decision will not affect your relationship with your doctor or the study team in any way.

If you want to stop being in this study, please let the research doctor know. That way you can find out what should be done about your normal medical care outside of the study. If you choose to stop, you can still be treated by the study doctor and be followed at the institution thereafter, or you can choose to be seen by another physician, it is your choice.

RIGHT OF INVESTIGATOR TO WITHDRAW

The investigator can withdraw you without your approval at any time if he or she believes it in your best interest. Possible reasons for withdrawal include if you develop new tumors in the brain between the first appointment and the Simulation appointment, and you are no longer eligible for the study.

COSTS AND COMPENSATION TO PARTICIPANTS

You and/or your health plan insurance company will need to pay for all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

NEW INFORMATION

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw at that time, your research doctor will make arrangements for your medical care to continue. If you decide to continue in the study, you may be asked to sign an updated consent form. Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/she will explain the reasons and arrange for your medical care to continue.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION

Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

If you refuse to provide authorization to disclose your protected health information, you will not be able to participate in this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, address, telephone number, and email address
- Social Security Number
- Related medical information about you like family medical history, allergies, current and past medications or therapies, and information from physical examinations, such as blood pressure reading, heart rate, temperature, and lab results
- All tests and procedures that will be done in the study

How we will protect and share your information:

- We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:

- Members of the research team and University of Utah Health Sciences Center
- The University of Utah Institutional Review Board (IRB), who reviews research involving people to make sure the study protects your rights;
- The FDA
- The OHRP
- Individuals with medical backgrounds who determine the effect that the study procedures may have on the disease
- Individuals who put all the study information together in report form
- The National Cancer Institute (NCI), a governmental agency that records and stores research information and provides funding for research.

If we share your identifying information with groups outside of the University of Utah, they may not be required to follow the same federal privacy laws that we follow. They may also share your information again with others not described in this form.

The purpose of collecting and sharing this information is to learn about how the study procedures may affect the disease and any study-related side effects.

Information disclosed to groups outside the University of Utah Health Sciences Center may no longer be covered by the federal privacy protections.

All identifying information such as your name and address will be kept private. You will be assigned a code number so that your name will not be used. The research team at the University of Utah will be able to link the code number to your name. In some instances, in order to ensure the scientific value of the study, the parties named before will be able to view your study record but will not be permitted to copy any identifying information contained in your record.

You have the right to see and reproduce your records related to the research study, and ask for corrections, for as long as this information is held by the study chair and/or the University of Utah.

However, in some studies, in order to ensure the scientific value of the study, participants are not able to view or reproduce their study records until the research has been completed with all participants in the study.

If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at the University of Utah.

What if I decide to Not Participate after I sign the Consent and Authorization Form?
You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

If you revoke this authorization, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

CONSENT

I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date/Time

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date/Time

WITNESS STATEMENT: (For Non-English Speaking Participants Only)

Consent was obtained from the participant using a short form for non-English speakers. The short form is available in the participant's language and this (long) consent form was read to the participant using an interpreter.

As a witness, I confirm that I was present for the complete consent process for this study. I confirm that the participant named above was read the information in this consent document in a language he/she understands and that the participant has agreed to take part in the research study.

_____
Name of Witness

_____ _____
Signature of Witness Date/Time

Information requested for federal grant reporting purposes *(optional)*

Sex/Gender

- ❑ **Male**
- ❑ **Female**

Ethnicity

Do you consider yourself to be Hispanic or Latino? (see definition below)

Hispanic or Latino. A person of Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture or origin, regardless of race.

Select one:

- ❑ **Hispanic or Latino**
- ❑ **Not Hispanic or Latino**

Race

What race do you consider yourself to be?
SELECT ONE OR MORE OF THE FOLLOWING:

- ❑ **American Indian or Alaska Native.** A person having origins in any of the original peoples of North America (including, Central or South America) who maintains cultural identification through tribal affiliation or community recognition.
- ❑ **Asian.** A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.
- ❑ **Black or African American.** A person having origins in any of the black racial groups of Africa.
- ❑ **Native Hawaiian or other Pacific Islander.** A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
- ❑ **White.** A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.
- ❑ **Unknown.**

❑ **Check here if you do not wish to provide some or all of the above information.**