NRG ONCOLOGY

NRG-BN009

(ClinicalTrials.gov Identifier NCT #04588246)

PHASE III TRIAL OF STEREOTACTIC RADIOSURGERY (SRS) OR HIPPOCAMPAL-AVOIDANT WHOLE BRAIN RADIOTHERAPY (HA-WBRT) FOR DISTANT BRAIN RELAPSE WITH BRAIN METASTASIS VELOCITY ≥4 BRAIN METASTASES/YEAR

Research Study Informed Consent Document

Study Title for Participants: (06-APR-2023) Comparing whole brain radiotherapy using a technique that avoids the hippocampus to stereotactic radiosurgery in people with cancer that has spread to the brain and come back in other areas of the brain after earlier stereotactic radiosurgery

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
(06-APR-2023)
Protocol NRG-BN009, Phase III Trial of Stereotactic Radiosurgery (SRS) or Hippocampal-Avoidant Whole Brain Radiotherapy (HA-WBRT) for Distant Brain Relapse With Brain Metastasis Velocity ≥4 Brain Metastases/Year (NCT 04588246)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you received stereotactic radiosurgery to treat cancer that spread to your brain, and now the cancer has returned in other areas of the brain.

Brain Metastasis Velocity (BMV) is a measure of how fast the cancer is spreading in your brain. If you have a BMV of four or higher, more treatment is needed to control the spread of cancer in your brain.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are

answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done? (06-APR-2023)

This study is being done to answer the following question:

Can we extend your life by using a type of radiation therapy called whole-brain radiation therapy that avoids the hippocampus to preserve memory plus the medication memantine that can decrease the risk of side effects of radiation on thinking and memory, to the usual treatment?

We are doing this study because we want to find out if HA-WBRT and memantine is better or worse than the usual approach for your brain cancer. The usual approach is defined as care most people get for cancer that has spread to the brain and returned in other areas of the brain after receiving SRS.

What is the usual approach to my brain cancer? (06-APR-2023)

The usual treatment for your brain cancer is stereotactic radiosurgery, or SRS, that delivers a high dose of radiation only to the small areas of cancer in the brain , but does not treat even smaller areas of cancer that cannot be seen in the brain.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study? (06-APR-2023)

If you decide to take part in this study, you will either get treatment with HA-WBRT and memantine, or you will get treatment with SRS.

The usual treatment, SRS, delivers a high dose of radiation only to the small areas of cancer in the brain but does not treat even smaller areas of cancer that cannot be seen in the brain. SRS is a single treatment over one day (or in some cases a few days) as an outpatient procedure.

If you receive HA-WBRT, you will receive it 5 days per week Monday through Friday for about 2 weeks as an outpatient procedure. Whole brain radiation therapy delivers a low dose of radiation to the entire brain including the normal brain tissue. Hippocampus avoidance during

whole-brain radiation therapy (HA-WBRT) decreases the amount of radiation that is delivered to the hippocampus which is a brain structure that is important for memory. The medicine memantine is also often given with whole brain radiation therapy because it may decrease the risk of side effects of radiation on thinking and memory.
You will receive memantine as a tablet by mouth for 6 months.

If you do not receive HA-WBRT plus memantine, you will receive the usual SRS treatment as described above.

After you finish your treatment, your doctor and study team will watch you for side effects and follow your condition. They will check you every 2 to 3 months for at least 1 year after you start treatment. If you are receiving memantine, your doctor will continue to see you in the clinic as needed.

What are the risks and benefits of taking part in this study? (06-APR-2023)

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer or preventing your cancer from coming back.

There is also a risk that you could have side effects from the study approach. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

Stereotactic radiosurgery (SRS)
- pain or discomfort during the treatment if a head frame is used
- the development of the same cancer in other areas of the brain

Whole brain radiation therapy with hippocampus avoidance (HA-WBRT)
- hair loss
- temporary scalp redness and drying
- tiredness

Memantine
- tiredness or drowsiness
- indigestion

There may be some risks that the study doctors do not yet know about.

Benefits
There is evidence that memantine and HA-WBRT is more effective in preventing the same cancer from growing in other areas of the brain compared to the usual approach of SRS. It is not possible to know now if the study approach will extend your life compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. This may mean slowly stopping the study treatment so that there is not a sudden unsafe change, risk to your health, etc. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (NRG Oncology). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study? (06-APR-2023)

The usual treatment for patients with cancer that has spread to the brain is a type of combined radiation and surgery treatment called stereotactic radiosurgery (SRS). The purpose of this study is to compare the usual treatment of SRS to HA-WBRT and memantine for patients with cancer that has spread to the brain and come back in other areas of the brain after earlier treatment with

SRS. HA-WBRT and memantine instead of the usual treatment could better control your brain cancer. But, it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better, the same, or worse than the usual approach. To decide if it is better, the study doctors will be looking to see if the study approach extends your life by about 1 year compared to the usual approach.

Memantine is FDA approved for treating dementia and is commonly used off-label (that is, for a purpose for which it is not FDA approved) for patients receiving whole-brain radiation therapy for cancer that has spread to the brain.

There will be about 350 people taking part in this study.

What are the study groups? (06-APR-2023)

This study has 2 study groups. You will be told which group you are in.

- **Group 1**

  If you are in this group, you will
  receive whole brain radiation therapy with hippocampal avoidance (HA-WBRT). HA-WBRT will be given to you as an outpatient for 5 days per week for about 2 weeks (about 10 treatments). The treatments last about 10 to 20 minutes, including the set-up. You will also be given the drug memantine, which has also been shown to preserve memory function. Memantine will be taken by mouth once or twice daily with water, with or without food. Memantine will be taken for up to 6 months. You will be given a medication diary to complete every cycle and a clinical trial wallet card with study information to provide to other healthcare providers if needed.

  There will be about 175 people in this group.

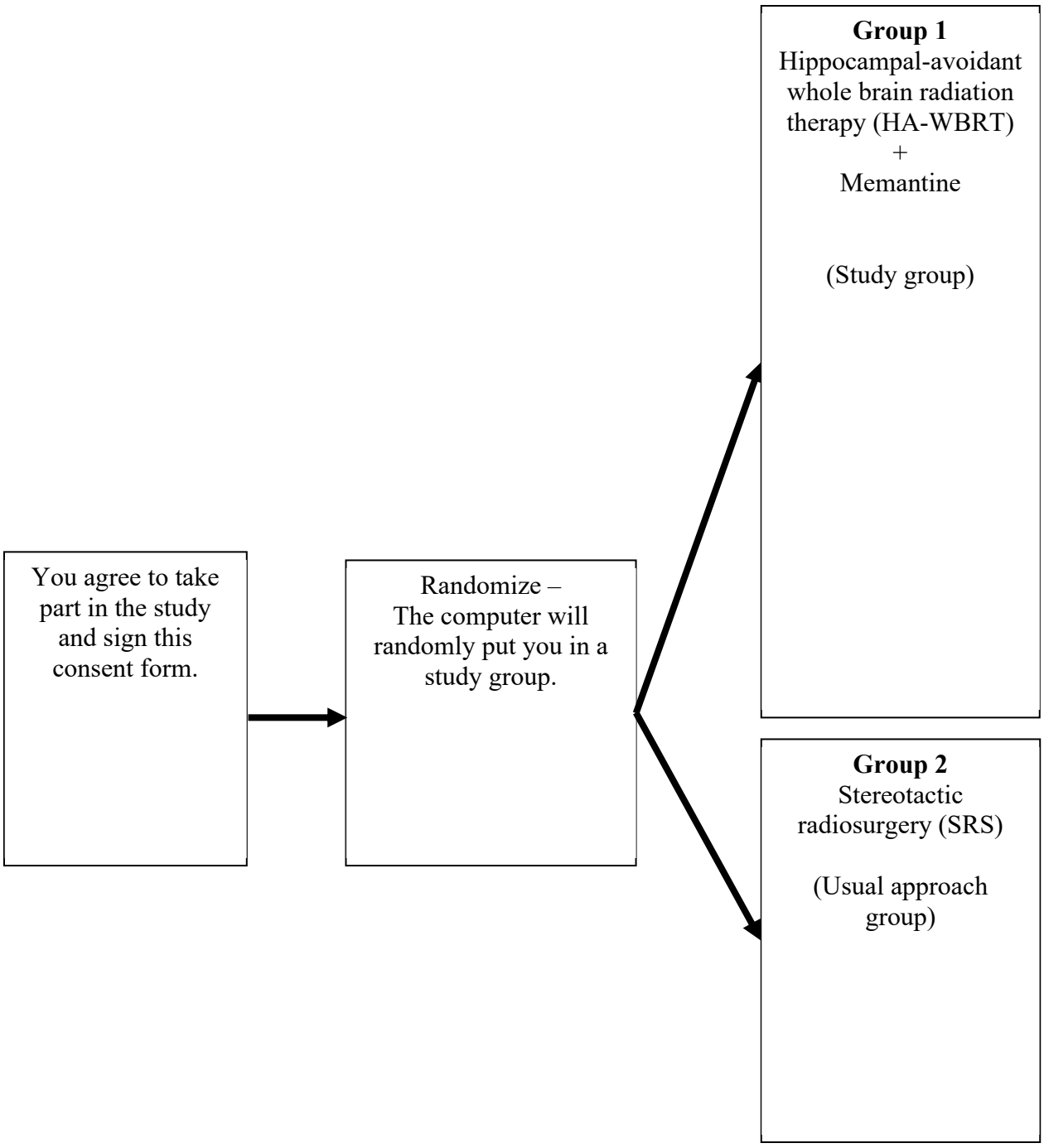
- **Group 2**

  If you are in this group, you will get the usual treatment of SRS. You will receive a high dose of radiation to the small areas of cancer in the brain. For most patients, the usual time on the SRS treatment machine is 30 to 90 minutes, but the entire procedure can take up to 4-6 hours including preparation time.

  There will be about 175 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



What exams, tests, and procedures are involved in this study? (06-APR-2023)

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

Neurocognitive Function Study

If you speak and understand English or live in Canada and speak French, you will be asked to complete 3 thinking measures to evaluate your thinking abilities, such as memory and following directions; these thinking measures will be administered by a trained test administrator in the clinic. Researchers will use this information to better understand what effects the treatments are having on your ability to think.

Since these thinking measures are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

You will be asked to complete the thinking measures 6 times during your regular office visits for the study:

- Before starting treatment (1 time); and
- At 2, 4, 6, 9, and 12 months after you start treatment (5 times)

The three combined thinking measures will take about 20-30 minutes to complete each time. You don't have to answer any question that makes you feel uncomfortable. There are no costs to you or your insurance.

Patient Reported Outcome Questionnaires

If you speak and understand English or live in Canada and speak French, you will be asked to fill out 3 questionnaires with questions about symptoms, your general health status, and your physical and emotional well-being. Researchers will use this information to better understand how patients feel and function during treatments and what effects the treatments are having.

Since these questionnaires are being used for research, the responses you provide will not be shared with your study doctor. Please also report any symptoms or difficulty with activities directly to your doctor or nurse right away.

You will be asked to fill out the questionnaires 6 times during your regular office visits for the study:

- Before starting treatment (1 time); and
- At 2, 4, 6, 9, and 12 months after you start treatment (5 times)

Each questionnaire will take about 5-10 minutes to complete each time you fill it out. The questionnaires will ask about things like your symptoms such as tiredness or weakness, your ability to complete physical tasks, and your emotional and social well-being. You don't have to answer any question that makes you feel uncomfortable.

You will have the option of completing the questionnaires by paper or by an electronic device (See *Section Below).

**Option for completing Patient Reported Outcomes Questionnaires with a personal electronic device*

If you speak and understand English or live in Canada and speak French you will have the option of completing the questionnaires on paper or by an electronic device. If you choose to complete the questionnaires with an electronic device, you will enter your answers to the questionnaires via a personal electronic device such as your smart phone or tablet. In some cases, a tablet may be provided to you at your health care institution. The use of your own electronic device on a cellular network may result in a nominal cost to your data plan. Regardless of the device you use, your answers and personal information will not be stored on the device. Your answers will be sent to the research database and will be kept private in the same way listed in the later section about who will see your medical records. Your e-mail address will only be used for this survey study and will not be used for mail or marketing purposes. NRG Oncology will not keep your e-mail address.

If you need help using the questionnaire application on your phone or tablet, ask for help at your study site. You don't have to answer any question that makes you feel uncomfortable. Someone may help you enter your answers in the device if you need.

All patients will complete the questionnaires before treatment on paper. After that, you can choose to complete the questionnaires for the remaining time points online or on paper. The choice is up to you. If you choose to complete the questionnaires using an electronic device, see Appendix I of this document for more information.

Please circle your answer:

I choose to use the electronic software for completing the Patient Reported Outcomes (PRO) questionnaires. I agree to fill out the PRO questionnaires electronically (after treatment has started).

YES **NO**

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The radiation and drug treatments used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use while you are receiving study treatment and, for patients receiving memantine, 90 days after the last dose of memantine.

Side Effect Risks

The radiation and drug treatments used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study treatments.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 – Possible side effects of memantine are listed in the tables below. Memantine is part of the experimental approach for treating this type of cancer.

Possible Side Effects of Memantine (Table Version Date: October 14, 2020)

Memantine is well-tolerated and is not associated with frequently occurring side effects.

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving memantine, from 4 to 20 may have:
• Headache • Constipation • Diarrhea • Pain • Shortness of breath • High blood pressure • Coughing • Nervousness • Changes in behavior • Confusion, Restlessness • Inability to obtain enough sleep • Depression • Tiredness, lack of energy • Vomiting

RARE, AND SERIOUS In 100 people receiving memantine, 3 or fewer may have:
• Seeing or hearing things that aren't there • Damage to kidney function

NOTE: Stevens Johnson Syndrome (SJS) is a severe skin rash with blisters and can involve the inside of mouth and other parts of the body and can include fever. Stevens Johnson Syndrome is very rare and, at this time, it is unknown if memantine causes this skin reaction. However, there have been reports of SJS while taking memantine. If you notice any skin reactions during treatment, inform your health care provider immediately.

Additional Drug Risks

Memantine could interact with other drugs. Please inform your study doctor about any other drugs you are taking.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Possible Side Effects of Radiation Therapy (06-APR-2023)

Study Group 1 – Possible side effects of hippocampal-avoidant whole brain radiation therapy (HA-WBRT) are listed in the tables below. HA-WBRT is part of the experimental approach for treating this type of cancer.

Possible Side Effects of Hippocampal-Avoidant Whole Brain Radiation Therapy (HA-WBRT)

COMMON, SOME MAY BE SERIOUS In 100 people receiving HA-WBRT, more than 20 and up to 100 may have:
• Hair loss • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving HA-WBRT, from 4 to 20 may have:
• Temporary scalp redness and drying • Nausea • Cataract formation • Dry mouth • Taste changes • Temporary ear and ear canal redness, plugging or drainage • Headaches • Memory loss, which may be permanent • Increased sleepiness (occurring four to ten weeks after radiation therapy is complete and lasting for several days up to two weeks) • The development of cancer in or near the hippocampus

RARE, AND SERIOUS In 100 people receiving HA-WBRT, 3 or fewer may have:
• Decreased brain function such as motor function (coordination/movement) • Severe damage to or death of normal brain tissue, which may require surgery to remove • Hardening of the arteries in the brain which rarely may lead to strokes many years after whole brain radiotherapy • A second new cancer caused by radiation, in the brain or nearby organs which rarely may occur many years after whole brain radiotherapy • Eye damage with the possibility of permanent blindness

Study Group 2 – Possible side effects of stereotactic radiosurgery (SRS) are listed in the tables below. SRS is the usual approach for treating this type of cancer:

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:
• Pain or discomfort during the procedure if a head frame is used • the development of the same cancer in other areas of the brain

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 • Memory loss, which may be permanent • Severe 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 • Eye damage with the possibility of permanent blindness

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
  - all medications and supplements you are taking
  - any side effects
  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.

- Write down in your medication diary when you take the study drug at home.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant while you are receiving study treatment or, if you are receiving memantine, within 90 days after your last dose.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of the stereotactic radiosurgery
- the costs of the whole-brain radiation therapy and memantine (if you are in Group 1)
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- Administration and completion of the neurocognitive function and Patient Reported Outcomes assessments.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- NRG Oncology
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research, including the Cancer Trials Support Unit (CTSU).
- The NCI's National Clinical Trials Network and the groups it works with to conduct research, including the Imaging and Radiation Oncology Core (IROC).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records

may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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 talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Known future studies

If you choose to take part in this optional study, researchers will collect blood for research on proteins and genes that may increase risk of developing new cancers in the brain or increase the chance of cognitive effects.

Unknown future studies

If you choose to take part in this optional study, blood will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by NRG Oncology and is supported by the NCI. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your blood samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may be passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

What is involved in this optional sample collection? (06-APR-2023)

If you agree to take part, here is what will happen next:

1. About 1 tablespoon of blood will be collected from a vein in your arm before you start radiation treatment and about 2 months after you start treatment.
2. Your sample will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. (~For non-US participants, adapt the following two sentences as needed. ~) There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.

2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*).

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for known future studies:

I agree that my samples and related health information may be used for the laboratory study described above.

YES NO

Samples for unknown future studies:

I agree that my samples and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Appendix I: Patient Instructions for Accessing the Patient Cloud Using Your Personal Device (06-APR-2023)

Downloading the Patient Cloud ePRO App

If you are using your personal device, and you do not have the Patient Cloud mobile app, use the following instructions. **When downloading the app, you must use the Apple ID or Google account associated with the device.** If the ePRO mobile app is already on the device, or if you are using a provider's device, you can skip this section. There are multiple versions of the ePRO mobile app available. Ensure that the correct version of the ePRO mobile app is downloaded.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to uniquely identify you on the ePRO Application, and to reset your password if needed. Your e-mail address will only be used for this survey study, and will *not* be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS (Apple smart devices):

1. An Apple ID is required for downloading the ePRO Patient Cloud mobile app.
2. Tap the *App Store* icon.
3. Search for "**Patient Cloud**" and follow the installation instructions to download the app with this icon:

For Android:

1. A Google account is required for downloading the ePRO mobile app
2. Tap the *Play Store* icon.
3. Search for "**Patient Cloud**" and follow the installation instructions to download the app with this icon:

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the ePRO mobile app.

Note: You must have an activation code to begin this process. *If you do not have an activation code, please contact your provider.*

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the ePRO mobile app.

1. If registering from the ePRO mobile app, tap "***Have an Activation Code?"*** on the **bottom of the log in page**. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap ***Activate***.
3. On the next page, read the instructions and tap ***Next***.
4. Read the privacy notice and tap ***I agree***. Then tap ***OK*** to confirm.
5. **Enter and confirm your email address**. Tap ***Next***.
6. **Enter and confirm your password**. Tap ***Next***.
7. **Choose a security question by scrolling** through the dropdown menu to display the question of your choice.
8. **Enter your response** to the security questions.
9. Tap ***Create my account*** to complete your registration.

If you registered on the ePRO mobile app, it automatically logs you out. If you registered on the web, you are presented with the option to download the ePRO mobile app. You can then proceed to log in with the credentials you created.

Logging in to the ePRO mobile app

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the ePRO mobile app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the ePRO mobile app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages (displays as 3 stacked horizontal bars).

1. Tap the options menu icon.
2. Tap *Reset Password*.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged into the ePRO mobile app, forms related to your study are displayed on the Tasks List page. Select a form, and complete and submit the form. New forms can appear on the Tasks List page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

To complete and submit form(s):

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you may be given the opportunity to review and change your responses prior to submitting.
3. If given the opportunity to review and update, review your responses by scrolling down the list; if you need to change an answer, tap the question to go back and change the answer.
4. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.