Mathematical Model-Adapted Radiation Fractionation Schedule for Patients with Recurrent Glioblastoma (MARS-Glio)

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Protocol Title: Mathematical Model-Adapted Radiation Fractionation Schedule for Patients with Recurrent Glioblastoma (MARS-Glio)

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A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have a primary brain tumor, called glioblastoma, which has returned or progressed after standard treatment. This research study is studying a new schedule of radiation therapy for recurrent glioblastoma as a possible treatment for this diagnosis. This radiation schedule is based on a new model for radiation resistance in glioblastoma.

The name of the radiation schedule involved in this study is:

- Re-irradiation for glioblastoma using a novel Mathematical Model-Adapted Radiation Fractionation Schedule

For purposes of this research, you will be referred to as a "participant".

It is expected that about 14 people will take part in this research study.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

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

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Feasibility Study, which means that this is the first time that investigators are examining this new radiation schedule for recurrent glioblastoma.

The FDA (the U.S. Food and Drug Administration) has approved radiation therapy as a treatment option for your disease.

This is the first time that this particular radiation schedule will be tested in humans. There many other studies which have tested different radiation schedules in glioblastoma.

In this research study, we are adapting a standard two-week schedule of radiation commonly used for recurrent glioblastoma using a mathematical model. This study uses the same total dose of radiation as standard treatments but breaks up the dose into different amounts daily to maximize tumor kill. We have used a new mathematical model to create this schedule of radiation. This model was created to better represent how glioblastoma cells can escape the damaging effects of radiation. Based on the results of several laboratory studies, it is possible that this model may result in improved outcomes compared to standard radiation schedules.

The primary question of this study is to see whether participants can complete this new radiation schedule at the scheduled times. In addition, we will follow patients to ensure that this treatment is safe. If this treatment proves feasible, we hope to compare this treatment directly with standard radiation schedules for newly diagnosed and recurrent glioblastoma.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Receiving standard treatment for glioblastoma, which involves radiation therapy over 2-3 weeks using daily radiation. In standard therapy, the dose does not vary from day to day. Standard treatment may also involve receiving chemotherapy, immunotherapy, or medical therapy recommended by your oncologist for recurrent glioblastoma.
- Taking part in another research study.
- Receiving no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused

by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

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

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

As part of this study, we will be using a new radiation schedule in which the dose of radiation and daily frequency of treatments changes during the treatment.

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

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

This screening visit will involve the following:

- **Clinical Exam*:*** You will have a physical exam and will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance Status:** We will evaluate how you are able to carry on with your usual activities.
- **Toxicity Assessment**: We will discuss any side effects or symptoms you may be experiencing from your tumor and/or treatment. If your symptoms warrant any particular treatment, we will discuss the plan at this time.
- **Questionnaire**: We will ask you to complete a scoring of your symptoms which we will compare with your symptoms after radiation treatment.
- **An assessment of your tumor** by one or more of the following standard assessment tools CT (Computerized Tomography) scan, or MRI (Magnetic Resonance Imaging).

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

On-Study Visits:

Radiation Planning

Prior to starting study treatment, you will need a radiation planning appointment, otherwise known as mapping or a simulation. This is standard for all patients treated in our department with your condition. During this visit, you will meet with a nurse to review your plan for treatment. This appointment will occur approximately 1-2 weeks prior to the start of your study treatment.

This visit will involve the following:

- **Radiation Planning*:*** During this visit you will undergo radiation planning. A customized plastic mask will be made for you to help keep your head in a stable position for all your treatments. After the mask is formed, we will obtain a CT scan of your head and neck, which we will use to plan our radiation treatments.
- **Photographs*:*** Photographs will be taken of your face for identification purposes as a safety check for our radiation treatments. This is part of our standard of care for all patients receiving radiation therapy. Care will be taken to ensure these are maintained securely within your medical record to protect your privacy.
- **Scans (or Imaging tests):** We will obtain a CT Scan of your head and neck while you are wearing your mask to use for your radiation planning. This is not a diagnostic scan and will not be used to assess your tumor but rather to map out the areas to be treated and avoided during radiation.

Radiation Treatments

You will be given a schedule for your radiation treatments. You should arrive at our department 20-30 minutes prior to your scheduled treatment time. Each treatment will take approximately 20-40 minutes. If you need any medication prior to treatment for pain, anxiety, discomfort, cough, or breathing difficulty, you should discuss this with your physician. As part of this study, it will be important to receive treatment as close to the scheduled time as possible.

These visits will involve the following:

- You will receive 10 days of radiation therapy over two weeks.
- Radiation therapy is delivered on Monday-Friday during standard clinic hours in our department. Each treatment may take 20-40 minutes.

Your schedule of radiation therapy will be as follows:

Week 1
- Monday – single dose of radiation
- Tuesday – single dose of radiation
- Wednesday – single dose of radiation
- Thursday – single dose of radiation
- Friday – single dose of radiation

Week 2
- Monday – single dose of radiation
- Tuesday – single dose of radiation
- Wednesday – three small doses of radiation therapy, spaced three hours and fifteen minutes apart
- Thursday – three small doses of radiation therapy, spaced three hours and fifteen minutes apart
- Friday – three small doses of radiation therapy, spaced three hours and fifteen minutes apart

- On the days you receive multiple doses of radiation therapy, you will have a break of three hours and fifteen minutes between each dose of radiation. You should plan for a long day at our facility on these days and may want to consider your travel for these days.

Visits During Radiation Therapy

Once you start your radiation treatment, you will be seen once per week by your physician. These visits are part of our standard care for all patients, and you will have a brief medical examination to review any ongoing symptoms or side effects from treatment.

These visits will involve the following:
- **Ongoing radiation therapy:** Daily treatments per your treatment schedule
- **Clinical Exam**
- **Performance status**
- **Toxicity Review**

First Follow up After Study Treatment Ends

Approximately 4 weeks after completing radiation therapy, you will return to our department and to your neuro-oncologist for a post-treatment follow-up visit. This is considered the standard of care for patients with your condition.

This visit will involve the following:

- **Clinical Exams**
- **Performance status**
- **Toxicity Review**
- **Questionnaire**
- **Scans (or Imaging tests):** We will assess your tumor using a CT of your head or an MRI of your brain.

Ongoing Follow Up After Study Treatment Ends

Approximately every 2-4 months for a total of 6 months after your radiation treatment ends, you will return to our department and to your neuro-oncologist for a routine follow-up visit. This is considered the standard of care for patients with your condition. Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study treatment.

In the case that you are unable to return to our clinic due to significant transportation limitations, you should be seen for follow-up visits by your local oncologist. It is important to tell the research team if you plan to do this.

Regardless of where you are seen, this follow-up visit will involve the following:

- **Clinical Exams**
- **Performance status**
- **Toxicity Review**
- **Questionnaire (if not being followed locally)**
- **Scans (or Imaging tests)**

Research Study Plan:

Sometimes it is easier to keep track of the visits and procedures by looking at a

chart. Please see the Research Study Plan below:

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Every 2-4 months*
	Screening	Radiation Planning	Radiation Start	Week 1 Visit	Week 2 Visit	4-week follow up	
Informed Consent	X						
Medical History (including assessment of development of seizures) & Physical Exam	X			X	X	X	X
Neurologic Exam	X			X	X	X	X
Karnofsky Performance Status (KPS)	X			X	X	X	X
CT or MRI	X	X				X	X
MDASI-BT	X					X	X
Toxicity Assessment	X			X	X	X	X
Radiation Planning		X					
Radiation Treatment			X	X	X		

**The MDASI-BT questionnaire is not required if you are being seen locally*
Abbreviations: MDASI-BT: M. D. Anderson Symptom Inventory – Brain Tumor survey

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

You will be followed on this research study for 6 months after you complete your radiation treatment. We will also aim to continue following your medical records outside of your visits for as long as possible to monitor your long-term outcomes and side effects.

You may be taken off the research study for many reasons including if:

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

- You are a female and become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed. The research doctor and research team will help arrange for your continued care. If you are removed from the research study, you may be followed for up to 6 months.

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

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

There are risks to taking part in any research study. One risk is that this radiation schedule does not help treat your disease or that it makes your condition or disease worse. Another risk is that you may experience side effects from radiation therapy treatments.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in this research study will be watched carefully for side effects. You will be monitored during the administration of study treatment to keep track of your symptoms. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.
Since the effect of the radiation with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take.

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

Risks Associated with Radiation Therapy:

Likely (More than 10% chance that this will happen)

- Tiredness – usually temporary and mild
- Scalp redness or soreness - usually temporary
- Hair loss – occasionally permanent
- Ear/ear canal reactions – possibly resulting in a short-term hearing loss
- Temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness (usually due to swelling in your brain from treatment)

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

- Headaches – usually temporary and controlled with over-the-counter medications
- Nausea or Vomiting– uncommon but treatable with prescription medications
- Dry mouth or altered taste
- Mild problems with thought processing or memory
- Skin irritation from tight mask
- Irritation of the eyes
- Permanent hearing loss
- Temporary worsening of existing neurological deficits, such as decreased vision, drowsiness, and weakness of your arms and legs
- Endocrine problems related to changes to the pituitary gland resulting in hormone imbalances like hypothyroidism (typically treatable with medication)
- Changes in normal bone, cartilage or brain tissue – typically not causing symptoms

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

- Tumor bleeding in your brain – a serious event that may require urgent head imaging and possible medical or surgical treatments.
- Severe local damage to normal brain tissue, a condition called necrosis (tissue deterioration). Necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment

- Severe problems with thought processing or memory
- Stroke
- Loss of speech
- Numbness, weakness, tingling or paralysis of parts of your body
- Seizures
- Injury to the eyes with the possibility of blindness
- Development of other tumors (either benign or malignant)
- Death - less than a 0.1% chance that this will happen

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

Risks Associated with MRI Scans:
When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the CT scan or MRI. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Our radiology department may decide to monitor your kidney function as part of their standard practice prior to receiving contrast for any scans. If there is any change in your kidney function, we may recommend that you have scans without contrast.
Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
Radiation therapy may affect a fetus. While receiving radiation therapy and for 6 months afterwards, you should not become pregnant or father a baby. If you will be nursing your baby, you should discuss this with your neuro-oncologist. We

can provide counseling about preventing pregnancy for either male or female study participants. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

The questionnaires used in this study may be upsetting. If you find the questionnaires upsetting, you may speak with the research doctor or ask to be referred for additional emotional support.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

We do not know if taking part in this study will help you. This study may help researchers learn information that could help people in the future.

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

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

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

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.
It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the radiation. In some cases, the abrupt stopping of your radiation treatment can have risks in itself and can complicate future treatments. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

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

You will not be paid for participating in this study.

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

J. WHAT ARE THE COSTS?

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

You or your insurance company will be charged for portions of your care during this research study that are considered standard of care for recurrent glioblastoma, including the course of radiation therapy. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

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

- Brigham and Women's Hospital: (617) 732-5524 or (617) 732-7485
- Dana-Farber Cancer Institute: (617) 632-3455

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

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

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

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

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to your insurance company. You will be responsible for deductibles and co-payments. There are no plans to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

L. WHAT ABOUT CONFIDENTIALITY?

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

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

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

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

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

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

Dana-Farber Cancer Institute

- Research Doctor: Shyam Tanguturi, MD: (617) 732-7560
- Study Coordinator: (617) 582-8925

24-hour contact: Dana-Farber Cancer Institute: Shyam Tanguturi, MD at (617) 632-0000 or page at (617) 632-0000 beeper 51085.

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

N. PRIVACY OF PROTECTED HEALTH INFORMATION

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

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

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

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

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug(s)

used in the study and for the purpose of this or other research relating the study drug(s) and their use in cancer;
- To better understand the diseases being studied and to improve the design of future studies; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

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

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

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

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

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

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

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

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

6. Statement of privacy rights:

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

O. DOCUMENTATION OF CONSENT

My signature below indicates:

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

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

Research Consent Form
for Biomedical Research
Dana-Farber/ Harvard Cancer Center
BIDMC/BCH/BWH/DFCI/MGH/Partners Network Affiliates OHRS 10.02.2017a

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

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

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

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

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

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

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

☐ 2b) did not give permission for the adult participant to participate

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