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Whole brain radiation versus stereotactic radiation in patients with 5-20 brain metastases: A phase III, randomized clinical trial

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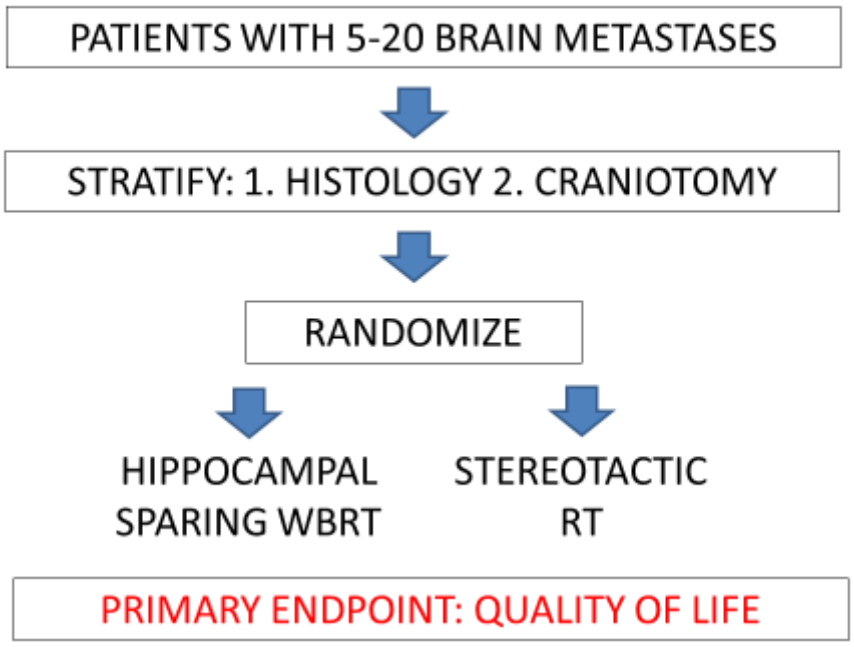
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SCHEMA


PATIENTS WITH 5-20 BRAIN METASTASES
STRATIFY: 1. HISTOLOGY 2. CRANIOTOMY
RANDOMIZE
HIPPOCAMPAL SPARING WBRT
STEREOTACTIC RT
PRIMARY ENDPOINT: QUALITY OF LIFE

1. INTRODUCTION

1.1 Study Disease

Brain metastases

Brain metastases are diagnosed in 10-50% of patients with cancer. The number of patients diagnosed with brain metastases in the United States per year is approximately 175,000, and is expected to increase over time.[1] The prognosis of patients with brain metastases is generally poor[2-4] and in patients with multiple intracranial lesions the paradigm for treatment generally relies on maximization of quality of life. Chemotherapy achieves unreliable and often poor control of brain metastases given limited penetration through the blood-brain barrier.[5] Targeted therapies, such as EGFR inhibitors[6] and ALK inhibitors[7] in non-small cell lung cancer, lapatinib in breast cancer,[8,9] and BRAF/MEK inhibitors[10] or immunotherapy[11] in melanoma, have shown significant promise in controlling intracranial disease but relatively few patients with brain metastases have tumors that can be reliably targeted by systemic agents. Accordingly, radiation represents the mainstay of therapy for most patients with brain metastases.

1.2 Rationale

Whole brain radiation

For most patients with greater than 4 brain metastases, whole brain radiation (WBRT), in which the entirety of the brain is treated with radiation, has historically been the standard treatment option. This treatment is generally delivered in 5-15 daily treatments given on weekdays over 2-3 weeks. WBRT can be associated with significant fatigue, neurocognitive changes, and other short- and long-term toxicities which can significantly impair quality of life.[12,13] Hippocampal sparing whole brain radiation has shown promising results in a single arm phase II trial but has not been tested against conventional whole brain radiation in a published randomized trial.[14]

Stereotactic radiation

Stereotactic radiation, in which a high dose of radiation is focused on the specific lesion(s) to be treated, with minimal dose to the surrounding brain, is an approach frequently used in patients with 1-4 brain metastases. Stereotactic radiation may carry a more modest short-term toxicity profile but does not treat subclinical disease elsewhere in the brain; stereotactic radiation has not been compared to WBRT in prospective, randomized trials involving patients with greater than four brain metastases. Stereotactic radiation can be delivered in 2 forms: stereotactic radiosurgery (SRS, which uses a single highly-targeted dose of radiation) and stereotactic radiotherapy (SRT, consisting of multiple smaller doses (fractions) of highly targeted radiation).

Comparisons of WBRT and stereotactic radiation

In clinical practice, most patients with 1-4 brain metastases will receive either stereotactic radiation or WBRT. There has never been a prospective study that has compared WBRT alone



versus stereotactic radiation alone. However, several trials have compared the combination of stereotactic radiation plus WBRT versus stereotactic radiation alone.[12,15,16] In all studies, the addition of WBRT to stereotactic radiation lowered the rate of distant intracranial failure but did not improve overall survival. In addition, the addition of WBRT was associated with a decrease in quality of life and neurocognition in several trials.[12,13]

There has been one randomized study comparing stereotactic radiation plus WBRT versus WBRT alone. A survival benefit was seen in the combined arm in patients with a single brain metastasis, thus establishing stereotactic radiation as the optimal radiotherapeutic modality for patients with a single lesion.[17] None of the above studies included patients with >4 brain metastases.

Stereotactic radiation in patients with >4 brain metastases

The use of stereotactic approaches for patients with >4 brain metastases has not been tested in a randomized controlled trial. Among patients with a very limited number of brain metastases, the risk of distant intracranial failure appears to increase as the number of brain metastases increases, leading to the need for closer surveillance and more salvage radiotherapeutic treatment when stereotactic treatment is employed as initial management. More recent data, however, suggest that rates of distant intracranial failure do not appear to be closely associated with the number of brain metastases present in patients with more than one lesion.[18] In addition, non-randomized but prospective studies of stereotactic radiation in patients with ≥5 brain metastases illustrate the potential viability and safety of stereotactic approaches for patients with large numbers of brain metastases, finding no difference in overall survival, deterioration of neurological function, local recurrence, new lesions, use of salvage radiation or surgery, or use of systemic anticancer agents between patients with 2-4 or 5-10 brain metastases.[19]

2. OBJECTIVES

2.1 Study Design

A randomized phase III clinical trial comparing hippocampal-sparing WBRT to stereotactic radiation in patients with 5-20 brain metastases

2.2 Primary Objectives

To test the hypothesis that, among patients with 5-20 brain metastases, post-treatment quality of life is superior for those treated with stereotactic radiation compared to those treated with WBRT

2.3 Secondary Objectives

To compare the following other endpoints between patients treated with WBRT and those treated with stereotactic radiation:

1. All-cause mortality

2. Death due to neurologic causes (defined as death due to progressive brain metastases on imaging associated with progressive neurologic symptomatology in the setting of systemic disease that has not progressed to a life-threatening nature)
3. Performance status
4. Incidence and time to detection of new brain metastases
5. Incidence and time to local recurrence
6. Incidence and time to development of radiation necrosis
7. Incidence and time to development of leptomeningeal disease
8. Incidence and time to progressive intracranial disease
9. Incidence and time to salvage craniotomy
10. Incidence and time to additional radiotherapeutic treatments after the initial course (stereotactic or WBRT)
11. Incidence and time to the development of seizures
12. Incidence and time to neurologic/neurocognitive decline
13. Steroid use

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria to be eligible for the study:

3.1.1. Participants must have a biopsy proven solid malignancy with untreated (by radiation) intracranial lesions radiographically consistent with or pathologically proven to be brain metastases
-Patients who have undergone prior systemic therapy for the management of brain metastases are eligible
- Patients who have undergone resection of one or more brain metastases but who have not yet started adjuvant radiotherapy are eligible for the study

3.1.2. Five-twenty intracranial lesions must be present on MRI of the brain

3.1.3. Age 18-80 years at diagnosis of brain metastases

3.1.4. Karnofsky performance status of at least 70 (See Appendix A)

3.2 Exclusion Criteria

3.2.1. Participants who have undergone prior radiation for brain metastases

3.2.2. Participants who cannot undergo a brain MRI

3.2.3. Participants who cannot receive gadolinium

3.2.4. Participants with stage V chronic kidney disease or end stage renal disease

3.2.5. Participants with widespread, definitive leptomeningeal disease

3.2.6. Participants with small cell lung cancer, lymphoma, or myeloma

3.2.7. Participants with a maximum tumor diameter exceeding 5 cm (if not resected)



3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. PRETREATMENT EVALUATIONS/MANAGEMENT

Patients presenting to a participating center who meet the eligibility criteria above will be identified by a radiation oncologist, medical oncologist, or neurosurgeon and offered participation in the study. All patients must have undergone an MRI of the brain with T1 post-contrast sequences (standard of care). No other pretreatment evaluations are required.

5. REGISTRATION PROCEDURES

5.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist. Informed consent will be obtained using a dedicated study consent form. Patients will be consented by the site PI or co-investigator.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). Registration cancellations must be made in OnCore as soon as possible.

Patients will be taken off the study if they withdraw consent, experience oncologic progression or other illness to the point that they can no longer tolerate the required visits, at the time of death, and at the discretion of the investigator.

5.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at DFCI by the Study Coordinator. All sites should call the Study Coordinator at 617-582-8925 to verify dose level availabilities. The required forms can be found in Appendix C.

Following registration, participants should begin protocol therapy within 21 days. Issues that would cause treatment delays should be discussed with the Overall PI. The Study Coordinator



should be notified of cancellations as soon as possible.

5.4 Registration Process for Other Investigative Sites

To register a participant, the documents listed in Section 3.7 of Appendix C should be completed by the research nurse or data manager and e-mailed to the Study Coordinator.

The research nurse or data manager at the participating site will then call or e-mail the Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled Subject Protocol Registration (SOP #: REGIST-101) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number and the registration arm to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration

6. RADIATION THERAPY

In order to be eligible to treat patients on this study, physicians must be credentialed for contouring and treatment planning for hippocampal sparing WBRT and stereotactic radiation. Separate credentialing will be utilized for hippocampal sparing WBRT versus stereotactic radiation. All radiation oncologists at an institution participating in the study may enroll patients, but patients cannot be treated until the treating physician is credentialed for the particular modality of radiation that the patient has been randomized to. The credentialing process will entail a review of the contours and radiation plan for the first enrolled case for a given radiation modality, prior to treatment, by the principal investigator, Dr. Ayal Aizer, and the physics chair, Dr. Fred Hacker, or their designee. If no significant edits to the contours are indicated and if all planning criteria listed below are met the treating physician will be credentialed for that modality of radiation. Contours/plans which require significant adjustments by the principal investigator or physics chair must be edited prior to treatment initiation; in such cases, the physician seeking credentialing will be provided with feedback and must submit a contour/plan for review prior to treatment of the next patient enrolled and randomized to the particular modality of radiation being utilized.

6.1 Whole brain radiation

A hippocampal sparing approach will be used. If a metastasis is in the hippocampus or within 5mm of the hippocampus, the entire metastasis plus a 2mm PTV will be treated to the prescription dose but the rest of the hippocampus on the affected side(s) will be spared as maximally as possible. Therefore some patients may undergo only partial hippocampal sparing unilaterally or bilaterally based on the distribution of the brain metastases.

6.1.1 Timing of Treatment: WBRT must begin within 21 days after registration and within 21 days of the MRI used for radiation planning. Patients cannot receive concurrent systemic chemotherapy with radiation. A minimum of three days is required between last administration of chemotherapy and initiation of radiation. A minimum of one day is required between last



administration of radiation and initiation of post-radiation chemotherapy. It will also be acceptable for patients to receive hippocampal sparing WBRT at a center not affiliated with the registering center if a DICOM file containing the entire radiation structure set, dose, and plan is reviewed and approved before treatment by the principal investigator of the study.

6.1.2 Dose: 30 Gy will be given in 10 fractions, prescribed to the PTV (as defined below). Radiation will be given in daily fractions, Monday-Friday. All metastases should be contoured and a 2mm PTV margin added. For patients who have rapidly growing gross disease an extra 0.1-1mm of PTV margin can be added at the discretion of the treating clinician to account for growth between planning and treatment; in such cases the time between planning and treatment should be minimized to the greatest extent possible. The PTV for each individual brain metastasis should be treated to 30 Gy in 10 fractions.

6.1.3 Physical factors: Treatment will be delivered using megavoltage machines with photon beams.

6.1.4 Simulation, Immobilization, Localization: The patient will be treated in the supine position. A thermoplastic mask will be used for immobilization. A CT simulation will be performed, with a maximum slice thickness of 1.25mm.

6.1.5 Treatment Planning and patient setup:

6.1.5.1 An MRI must be obtained with T1 sequences (e.g. spoiled gradient (SPGR) or magnetization prepared rapid gradient echo (MPRAGE) sequences) with a maximal slice thickness of 1.25 mm. Contouring software capable of 3D reformatting is required. All metastases must be contoured. The PTV brain will be defined as the whole brain + meninges minus hippocampal avoidance regions (hippocampi + 5mm). The inferior border of the target will be at the inferior aspect of C1. In patients with metastases near C1 a lower inferior border can be utilized (e.g. inferior aspect of C2). Volumetric modulated arc therapy will be employed. At least 90% of the PTV brain should be covered by the prescription dose. If this cannot be obtained, at least 85% of the PTV brain should be covered by the prescription dose. The minimum dose to 98% of the PTV brain should be ≥25 Gy. If this cannot be obtained the minimum dose to 95% of the PTV brain must be ≥25 Gy. The maximum dose to 2% of the PTV brain (D2%) should be 35 Gy. If this constraint cannot be met then it will be acceptable for the D2% to be ≤37.5 Gy. For all individual brain metastases in patients receiving hippocampal sparing WBRT, at least 99% (ideal) / 98% (at minimum) of the PTV (of each individual brain metastasis) should be covered by the prescription isodose line (30 Gy). The entire PTV for each brain metastasis should be covered by 90% (ideal) / 85% (at minimum) of the prescription dose. Daily set up with cone beam CT or stereoscopic KV imaging and use of a couch capable of making linear and rotational corrections is mandated. Patients who have received prior radiation which deposited scatter dose to a current intracranial target (e.g. prior head and neck radiation) may have dose / fractionation / field adjustments at the discretion of the treating clinician and overall PI.



6.1.6 Critical structures:

6.1.6.1 Bilateral hippocampal contours will be generated on MRI per the RTOG contouring atlas (https://www.rtog.org/corelab/contouringatlases/hippocampalsparing.aspx) and expanded by 5mm to generate avoidance regions. The D100% of each hippocampus should be ≤9 Gy; the maximum dose (to 0.035cc) should be ≤16 Gy; if these constraints cannot be met then it will be acceptable for the D100% to be ≤10 Gy and the maximum dose (to 0.035cc) to be ≤17 Gy. If a patient has a metastasis in the hippocampus tumor coverage will be prioritized over hippocampal sparing; the uninvolved hippocampus will be spared maximally but no specific D100% or maximum dose to the hippocampus are mandated. Dose to the eyes, optic nerves and chiasm should be limited to < 35 Gy (ideal) or 37.5 Gy (at minimum) as a point dose.

6.1.7 Management of Radiation Dose to the Patient from Daily Localization Scans:

6.1.7.1 Cone beam CT or stereoscopic KV imaging will be used in this study. The doses used for daily localization images are extremely low. MV imaging (which deposits a markedly greater radiation dose) will not be employed in this study.

6.1.8 Quality Assurance

6.1.8.1 WBRT Documentation Requirements

For patients treated at BWH,Dana-Farber Cancer Institute, or South Shore Hospital the institution will archive treatment prescription and verification images for later review by the study chair if requested.

6.1.8.2 Radiation Quality Assurance Reviews

RT quality assurance reviews will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by the study chair.

6.1.9 Radiation Adverse Events

All participants will be seen weekly by their treating radiation oncologist while undergoing therapy. Any observations with respect to symptoms/side effects that are possibly, probably or definitely related to brain metastases or brain-directed radiation will be followed for adverse event (AE) reporting. See section 8 for listing of particular AEs that will be monitored. This is not an all-inclusive list, and any AE that is considered by the treating physician to be related to brain metastases and/or brain-directed radiation will be followed with attributions and grading according to CTCV 4.0. Routine solicited AEs not considered by treating physicians to be related to brain metastases or radiation to the brain will be treated according to institutional guidelines and managed by the patient's oncology team in the best clinical judgment of the responsible physician.



Clinical discretion may be used in managing radiotherapy-related side effects.

6.1.10 Radiation Adverse Event Reporting

See Section 6.1.9. for Adverse Events information.

6.2 Stereotactic radiation

6.2.1. Timing of Treatment: Stereotactic radiation must begin within 21 days after registration and within 14 days of the MRI used for radiation planning. Patients cannot receive concurrent systemic chemotherapy with radiation. A minimum of three days is required between last administration of chemotherapy and initiation of radiation. A minimum of one day is required between last administration of radiation and initiation of post-radiation chemotherapy. Radiation must be delivered at an enrolling center; stereotactic radiation at outside centers will not be permitted.

6.2.2. Dose: Lesions <2 cm in maximum diameter will be treated with stereotactic radiosurgery, generally 20 Gy in 1 fraction. Lesions between 2.0 and 2.5-3.0 cm in maximum diameter will generally be treated to 18 Gy in 1 fraction. The volume receiving 12 Gy (V12) should be limited to <10cc; dose reductions are acceptable if the V12 constraint cannot be met via replanning, with a minimum dose of 16 Gy. Lesions >2.5-3 cm will generally be treated with stereotactic radiotherapy to 30 Gy in 5 fractions given on consecutive weekdays. Surgical cavities can be treated to 15-20 Gy in one fraction (based on size and V12 criteria above) or, for larger cavities, 25 Gy (gross total resection) or 30 Gy (subtotal resection) in 5 fractions on consecutive weekdays. Patients with simultaneous metastases that require 1 fraction and 5 fractions can be treated concurrently. If a metastasis that would be treated normally with SRS is adjacent to a metastasis that must receive SRT (so that a significant degree of scatter dose from the SRT field will include the potential SRS field) it is acceptable for the treating investigator to treat both metastases with SRT. Patients who have received prior radiation which deposited scatter dose to a current intracranial target (e.g. prior head and neck radiation) may have dose / fractionation adjustments at the discretion of the treating clinician and overall PI.

6.2.3. Physical factors: Treatment will be delivered using megavoltage machines with photon beams.

6.2.4. Simulation, Immobilization, Localization: The patient will be treated in the supine position. A tightly fitting thermoplastic mask will be employed for immobilization. A CT simulation will be performed, with a maximum slice thickness of 1.25mm.

6.2.5. Treatment Planning and patient setup: The GTV will cover the metastasis (or cavity plus any residual tumor in patients who have had neurosurgical resection) as identified by contrast enhanced MRI and CT (contrast optional) obtained within 14 days of the treatment initiation date. The MRI must be obtained with a T1 post contrast sequence with a maximal slice thickness of 1.5 mm (e.g. spoiled gradient (SPGR) or magnetization prepared rapid gradient echo (MPRAGE) sequences). Contouring software capable of 3D reformatting is required. No CTV is



to be used. The PTV will be 1mm for intact lesions and 2mm for cavities. For patients who have rapidly growing gross disease an extra 0.1-1mm of PTV margin can be added at the discretion of the treating clinician to account for growth between planning and treatment; in such cases the time between planning and treatment should be minimized to the greatest extent possible. Treatments will be delivered through VMAT using a single isocenter for PTV volumes >1.0 cm in maximum diameter. For PTV volumes with a maximum dimension of 0-1.0 cm in diameter either VMAT, circular collimators, or multiple static fields will be acceptable. More than one isocenter can be used if deemed as indicated by the treating physician. The prescription will generally be normalized to the 60-95% isodose line but alternative normalizations (e.g. using a lower normalization to maximize dose fall off) can be utilized by the treating physician if deemed appropriate.. 100% of the GTV should be covered by the prescription dose. At least 99% (ideal) / 98% (at minimum) of the PTV should be covered by the prescription isodose line. The entire PTV should be covered by 90% (ideal) / 85% (at minimum) of the prescription dose. Daily set up with cone beam CT or stereoscopic KV imaging and use of a couch capable of making linear and rotational corrections is mandated. Use of real-time motion management with 3-dimensional surface monitoring is optional but encouraged.

6.2.6. Critical structures:

Dose constraints for stereotactic radiosurgery to critical structures will be as follows:

Table 1. Dose constraints for stereotactic radiosurgery

Organ at Risk	Tolerance	Dose Modification Regimen
Eyes, Optic Nerves, Optic Chiasm	Point dose ≤8 Gy	If point dose >8 Gy, undercover PTV while maintaining 100% GTV coverage. If not achievable, dose reduce GTV to highest dose which meets optic constraint, through 16 Gy (15 Gy for cavity in which gross total resection has been achieved). If 100% of GTV cannot be safely covered by 16 Gy (15 Gy for cavity in which gross total resection has been achieved), then an acceptable variation will be to convert to stereotactic radiotherapy – see Table 2
Brainstem (defined as brainstem volume minus GTV)	Dose to 0.035cc ≤12 Gy	If dose to 0.035cc >12 Gy, undercover PTV while maintaining 100% GTV coverage. If not achievable, dose reduce GTV to highest dose which meets brainstem constraint, through 16 Gy (15 Gy for cavity in which gross total resection has been achieved). If 100% of GTV cannot be safely covered by 16 Gy (15 Gy for cavity in which gross total resection has been achieved), then an acceptable variation will be to convert to stereotactic radiotherapy – see Table 2
Volume of normal brain	≤10cc	If the V12 is >10cc, undercover PTV while



(less the GTV) receiving >12 Gy (per individual lesion, called the V12)		maintaining 100% GTV coverage. If not achievable, dose reduce GTV to highest dose which meets constraint, through 16 Gy (15 Gy for cavity in which gross total resection has been achieved). If 100% of GTV cannot be safely covered by 16 Gy (15 Gy for cavity in which gross total resection has been achieved), then an acceptable variation will be to convert to stereotactic radiotherapy – see Table 2
Normal brain less the GTV (for entire brain)	Mean <5 Gy	Administer stereotactic radiation on two or more consecutive weekdays rather than a single day

Dose constraints for stereotactic radiotherapy to critical structures will be as follows:

Table 2. Dose constraints for stereotactic radiotherapy (5 fractions)

Organ at Risk	Tolerance	Dose Modification Regimen
Eyes, Optic Nerves, Optic Chiasm	Point dose of 25-27 Gy	If point dose >25-27 Gy undercover PTV while maintaining 100% GTV (30 Gy in 5 fractions if gross disease; 25 Gy in 5 fractions if gross total resection has been achieved) coverage. If not achievable, dose reduce GTV to highest dose which meets constraint, through 23 Gy in 5 fractions. 100% of GTV should always receive at least 23 Gy in such a scenario.
Brainstem (defined as brainstem volume minus GTV)	Dose to 0.035cc ≤28 Gy	If dose to 0.035cc >28 Gy, undercover PTV while maintaining 100% GTV coverage (30 Gy in 5 fractions if gross disease; 25 Gy in 5 fractions if gross total resection has been achieved). If not achievable, dose reduce GTV to highest dose which meets brainstem constraint, through 23 Gy in 5 fractions. 100% of GTV should always receive at least 23 Gy in such a scenario.

The hippocampi should be contoured for patients undergoing stereotactic radiation to the brain so that hippocampal dose can be formally recorded but no specific constraints are mandated.

6.2.7. Management of Radiation Dose to the Patient from Daily Localization: Cone beam CT or stereoscopic KV imaging will be used in this study. The doses used for daily localization images are extremely low. MV imaging (which deposits a markedly greater radiation dose) will not be employed in this study.



6.2.8 Quality Assurance

6.2.8.1 Stereotactic Radiation Documentation Requirements

The institution will archive treatment prescription and verification images for later review by the study chair if requested.

6.2.8.2 Radiation Quality Assurance Reviews

RT quality assurance reviews will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by the study chair.

6.2.9 Radiation Adverse Events

All participants will be seen by their treating radiation oncologist while undergoing therapy. Any observations with respect to symptoms/side effects that are possibly, probably or definitely related to brain metastases or brain-directed radiation will be followed for adverse event (AE) reporting. See section 8 for listing of particular AEs that will be monitored. This is not an all-inclusive list, and any AE that is considered by the treating physician to be related to brain metastases and/or brain-directed radiation will be followed with attributions and grading according to CTCV 4.0. Routine solicited AEs not considered by treating physicians to be related to brain metastases or radiation to the brain will be treated according to institutional guidelines and managed by the patient's oncology team in the best clinical judgment of the responsible physician.

Clinical discretion may be used in managing radiotherapy-related side effects.

6.2.10 Radiation Adverse Event Reporting

See Section 6.2.9 for Adverse Events information.

7. SURGERY

This study does not involve surgery. There may be patients who have undergone resection of a brain metastasis prior to enrollment on the study.

8. ADVERSE EVENTS

Toxicity assessments will be performed using the active version of the NCI CTCAE which is available at:

http://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm



Grade 1-2 fatigue will be managed supportively. Activity will be encouraged.
Grade 3 fatigue can be managed per above, with the additional of low-dose dexamethasone and/or methylphenidate 2.5-5.0 mg daily, as needed.

Grade 1-2 nausea can be managed with as-needed antiemetics such as Zofran 8 mg prn, steroids (dexamethasone preferred, e.g. 2 mg PO BID), and hydration.
Grade 3 nausea can be managed per above with the addition of intravenous fluids and electrolyte repletion. Hospitalization and a treatment break can be considered.

Grade 1 headache can be managed with Tylenol 650 mg BID and consideration of low-dose dexamethasone (2 mg PO BID)
Grade 2 headache can be managed per above, with narcotics as needed.
Grade 3 headache can be managed per above, with consideration of high-dose dexamethasone (4 mg PO TID) and a treatment break.

Symptomatic edema can be managed with dexamethasone (2 mg PO BID) at discretion of treating physician.

Seizures will be managed with antiepileptic drugs, consideration of a treatment break, and referral to Neuro-oncology or admission, depending on the nature and severity of the episode.

Any observations with respect to symptoms or side effects that are possibly, probably, or definitely related to brain metastases or radiation to the brain will be followed for AE reporting.

9. PARTICIPANT ASSESSMENTS

Table 3 presents the schedule of treatment and follow up visits. Follow up visits should occur within 21 days of the scheduled day (in reference to the start of radiation). If a participant fails to appear for a visit, the investigator will make every attempt to contact them and determine the reason for the missed visit. The primary endpoint (quality of life, as per the MDASI-BT: M. D. Anderson Symptom Inventory – Brain Tumor survey) will be assessed at baseline, 3 weeks after initiation of radiation, and 2, 4, 6, 8, 10, and 12 months post-treatment (a month will be considered 30.4 days). Karnofsky Performance Status (KPS) and vitals will also be assessed at baseline, 3 weeks after initiation of radiation, and 2, 4, 6, 8, 10, and 12 months post-treatment. Toxicity review will consist of a history at each visit to monitor for relevant toxicity as described in section 11.7.1. MDASI-BT, KPS, and toxicity review for the 3 week visit can be obtained in person or over the phone by a physician or trained study staff. If the 3 week visit is conducted via telephone call, vitals need not be obtained. Neurologic/neurocognitive assessments (Hopkins Verbal Learning Test - Revised (HVLT-R), Trail Making Test Part A and B (TMT), Controlled Word Association Test (COWAT), Mini-Mental Status Examination (MMSE), Cognitive Functioning Subscale of the Medical Outcomes Scale (MOS), Grooved Pegboard) and an assessment of activities of daily living (the Barthel Index) will be conducted at baseline and at 4 and 12 months post treatment; this cognitive battery takes 30-45 minutes to complete. MRIs of the brain will be obtained every two months. For patients who clinically require more or less frequent MRIs of the brain (e.g. new symptoms warranting evaluation) / assessments the MRI



schedule can be adapted if approved by the Principal Investigator. MRIs of the brain will define the dimensions (size) in the axial plane and location in the brain (1. left vs right; 2. region of the brain – frontal, temporal, parietal, occipital, basal ganglia, thalamus, brainstem, cerebellum). A participant will be deemed lost to follow-up only after at least 3 attempts to contact him/her have been made over a 3-week period. MRIs of the brain will generally be obtained on the same day as the study visit but if necessary it is acceptable to unlink the MRI and study visits by a period of up to 2 weeks.

The usual post-radiation clinical care for our patients involves visits every two months in which MRIs are obtained and the MDASI-BT is performed as part of an institution-wide effort to collect patient-reported outcomes. Follow-up data from these visits will continue to be collected after active participation in the study concludes. Therefore, participants will be followed until death or loss to follow up, as part of our typical follow up care, and their relevant outcome data retrospectively collected during that time. If a participant transitions to hospice care during the 12 month active follow up period, usual clinical care and all study questionnaires will cease, and the participant will be retrospectively evaluated for relevant outcome data.

The length of follow up for the primary outcome measure (quality of life using the MDASI-BT) is 6 months. The length of follow up for the neurocognitive secondary endpoint will be 12 months. The length of follow up for all other endpoints will be until death or loss to follow up. This is because after 12 months, the usual clinical care for patients with brain metastases involves a radiation oncology visit, history, and an MRI brain every two-four months until death or other loss to follow up. All secondary endpoints (with the exception of neurocognition) are assessed as part of usual clinical care. In addition, as part of an institutional effort to collect patient report outcome measures (PROMs) we collect a MDASI-BT, the same instrument used as the primary endpoint of the study, to assess quality of life at every visit for all patients regardless of their participation in research.



Table 3. Study Calendar

	Pre-Treatment	Weeks 1-3 (treatment period)	3 weeks after initiation of radiation*	2 months*	4 months*	6 months*	8 months*	10 months*	12 months*
Treatments, evaluations, and follow up studies									
Informed consent	X								
Medical history (including assessment of development of seizures)	X	X	X	X	X	X	X	X	X
Complete physical exam (if indicated based on history)	X								
Neurologic exam (if needed based on history)	X		X	X	X	X	X	X	X
Karnofsky Performance Status	X	X	X	X	X	X	X	X	X
Toxicity Review	X		X	X	X	X	X	X	X
MDASI-BT	X		X	X	X	X	X	X	X
Neurocognitive Assessment	X				X				X
MRI brain (assessment of all secondary radiographic endpoints)	X			X	X	X			X

Radiation planning begins		X							

Abbreviations: MDASI-BT: M. D. Anderson Symptom Inventory – Brain Tumor survey
*Visits must occur within 30 days of the exact date.

10. DATA COLLECTION

Data Item	Timing
MRI brain report	At registration
Pathology report	At registration
MDASI-BT	At specified intervals above
Neurologic/neurocognitive Assessment	At specified intervals above in addition to a 12 month post treatment evaluation
Radiation begins	Two weeks from registration

Data entry must occur within 2 weeks of the patient visit when possible. Follow-up imaging data and specific details of hippocampal sparing and stereotactic radiation may be entered at closure to accrual.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

Primary endpoint

The primary outcome measure will be neurologic quality of life, assessed by the MDASI-BT index (Appendix B), ascertained at the time of study enrollment, 3 weeks after initiation of radiation, and every 2 months thereafter for 12 months in total. We will conduct a longitudinal / repeated measures analysis to determine whether quality of life (average of (1) the mean MDASI-BT symptom severity score for items 1-22 and (2) the mean MDASI-BT symptom interference score for items 23-28 in APPENDIX B between 0-6 months) is different among patients assigned to WBRT versus stereotactic radiation. Therefore, the primary endpoint will be equally weighted to assess both (1) symptom severity and (2) symptom interference, both derived from the MDASI-BT. A permuted block randomization will be employed. The analysis for all endpoints will be based on the intention to treat.

Secondary endpoints

Secondary outcomes and analytic techniques to compare patients treated with WBRT versus stereotactic radiation will include:



1. All-cause mortality (Kaplan-Meier plot, log-rank test, Cox regression)
2. Death due to neurologic causes (cumulative incidence plots, Gray's test, Fine and Gray's competing risks regression)
3. Performance status (longitudinal regression)
4. Incidence and time to detection of new brain metastases (Kaplan-Meier plot, Cox regression)
5. Incidence and time to local recurrence (Kaplan-Meier plot, Cox regression)
6. Incidence and time to development of radiation necrosis (Kaplan-Meier plot, Cox regression)
7. Incidence and time to development of leptomeningeal disease (Kaplan-Meier plot, Cox regression)
8. Incidence and time to progressive intracranial disease (Kaplan-Meier plot, Cox regression)
9. Incidence and time to salvage craniotomy (Kaplan-Meier plot, Cox regression)
10. Incidence and time to additional radiotherapeutic treatments after the initial course (Kaplan-Meier plot, Cox regression)
11. Incidence and time to the development of seizures (Kaplan-Meier plot, Cox regression)
12. Incidence and time to neurologic/neurocognitive decline (decline in any of the following tests: Hopkins Verbal Learning Test - Revised (HVLT-R), Trail Making Test Part A and B (TMT), Controlled Word Association Test (COWAT), Mini-Mental Status Examination (MMSE), Cognitive Functioning Subscale of the Medical Outcomes Scale (MOS), Grooved Pegboard, Barthel Index as assessed via longitudinal regression) with specific domains outlined here:
    a. Learning/memory: HVLT-R
    b. Processing speed: TMT-A
    c. Executive function: TMT-B
    d. General neurocognitive: MMSE, MOS
    e. Verbal fluence: COWAT
    f. Fine motor control: Grooved pegboard
    g. Functional independence: Barthel index
13. Steroid use (longitudinal regression)
14. Quality of life beyond that assessed in the primary endpoint (e.g. assessments beyond 6 months)

Our power calculation will be based on the hypothesis that stereotactic radiation will provide greater quality of life (AUC curve) than WBRT, relative to the standard deviation. We will account for censoring and death by tabulating the quotient of the achieved quality of life divided by the maximum predicted quality of life (baseline quality of life multiplied by months of follow up). All tests are two sided, with a type 1 error rate of 0.05. We will stratify the randomization and analysis based on tumor histology (breast, lung, melanoma, other) and receipt of neurosurgical resection vs not;196 patients will be required in order to detect a meaningful difference in quality of life using the above approach, as discussed in 11.2. The study will be analyzed based on the intent-to-treat principle.



11.2 Sample Size, Accrual Rate and Study Duration

Prior literature has estimated compliance with quality of life surveys in patients with brain metastases to be approximately 50% at 6 months[13] and that the median survival for such patients would be approximately 8 months.[15] We are assuming non-compliance of the QOL assessments over time, due largely to rapid disease progression and/or death, to be equal in the stereotactic and WBRT groups and to approximate the following:

Baseline Compliance: 100%
3-week Compliance: 85%
4-month Compliance: 70%
6-month Compliance: 45%
8-month Compliance: 20%

Patients will be assessed via MDASI-BT at baseline, 3 weeks after initiation of radiation, and every 2 months post-baseline up to and including 12 months but it is expected that very few patients will be assessable beyond 12 months. The primary analysis, therefore, will focus on the within-patient weighted average difference in MDASI-BT scores in the first 6 months post-baseline (that is, the within-patient average of week 3 and months 2, 4 and 6) adjusted for baseline (i.e., subtracting each patient's baseline MDASI-BT score). Hence, the outcome for the primary comparison will be the average of [3 wk, 2 mo, 4 mo, 6 mo] - [baseline] for each patient. For patients with fewer than 4 follow-up MDASI-BT assessments, the average of two or three scores minus baseline or simply the difference of the single score minus baseline will be used with the following weightings (inverse to the associated SE for 1 or the average of 2, 3, or 4 scores per patient): four assessments: sqrt(4)=2.0; three assessments: sqrt(3) = 1.73; two assessments: sqrt(2) = 1.41; one assessment: 1.0. The primary analysis will be conditional on patients with at least a 3-week assessment, hence the overall sample size needs to be inflated by 1/.85 = 1.18.

For symptom severity, assuming, conservatively, an individual MDASI-BT standard deviation of 2 points and interest in detecting a clinically meaningful change of one-half the difference in scores observed between good and poor performance status (PS) patients documented in a similar population (1.4 points),[20] the target difference corresponds to a change between treatment groups of 0.7 points. We also assume that the average patient will have a within-patient SD of 0.69*2 = 1.38 for post-baseline assessments based on the compliance assumptions above and the averaging of the number of expected assessments per patient that will form the primary endpoint. Taking as the primary measure the difference between post-baseline average and baseline MDASI-BT, and assuming conservatively a correlation of 0.60 between pre- and post-baseline assessments, the SD of the primary outcome measure is expected to be around 1.6 points. This leads to a target effect size of 0.44 (0.70/1.6). In order to have 80% power to detect an effect size of 0.44 between the primary endpoint across the two treatment groups (stereotactic versus WBRT), the study will require 83 patients per arm assessed at least once after treatment initiation using the weighted analysis and a two-sided significance level of 0.05. After inflating as above for patients who are assessed at baseline but drop out before 3 weeks, the total sample size is 98 patients per arm or 196 patients total. Incorporation of symptom interference into the primary



endpoint is not expected to change this estimate meaningfully.

In addition to the average change from baseline analysis, traditional timepoint-by-timepoint analyses (adjusted for baseline) will also be completed to compare the treatment arms with respect to MDASI-BT over time. Power for these analyses will differ depending upon the associated non-compliance over time.

At the initial conception of the protocol, we estimated that the Department of Radiation Oncology at Brigham and Women's Hospital / Dana-Farber Cancer Institute treats 500 patients per year with new brain metastases. Of these, approximately 30% will have 5-20 brain metastases and otherwise be eligible for our study. If 30% of patients offered participation on the trial accept enrollment, then we will be able to accrue 50 patients/year to the study. We anticipate that the study will take 4 years to accrue to goal. Up to an additional 12 months of follow-up will be required on the last participant accrued to observe the participant's response after the completion of protocol therapy, for a total study duration of 5 years.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	5	+	5	=	10
Not Hispanic or Latino	93	+	93	=	186
Ethnic Category: Total of all subjects	98 (A1)	+	98 (B1)	=	196 (C1)
Racial Category					
American Indian or Alaskan Native	1	+	1	=	2
Asian	5	+	5	=	10
Black or African American	5	+	5	=	10
Native Hawaiian or other Pacific Islander	1	+	1	=	2
White	86	+	86	=	172
Racial Category: Total of all subjects	98 (A2)	+	98 (B2)	=	196 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

11.3 Stratification Factors

We will stratify the analysis based on tumor histology (breast, lung, melanoma, other) and receipt of neurosurgical resection vs not. Stratification will be based only on these two factors. We will not perform interim monitoring and efficacy determination for each stratum

individually.

11.4 Interim Monitoring Plan

In a retrospective series of 186 patients with 5-15 brain metastases assessed for survival-based endpoints treated at DFCI/BWH largely with WBRT, it was observed that the neurologic death rate was 18% at 1 year. We will monitor both adverse events with an early stopping rule on the stereotactic arm as follows. If at any time 8 or more of the first 27 patients assigned to SRS experience neurologic death before 1 year, the study will halt for re-evaluation of the safety of this regimen. In order to ensure adherence to this rule, the cause of death (systemic vs. neurologic) will be recorded for each patient who dies. The study team will alert the statistician whenever a neurologic death is observed within one year of enrollment. Death due to progressive neurologic disease will be defined as marked, progressive radiographic progression in the brain accompanied by corresponding neurologic symptomatology in the absence of systemic disease progression / systemic symptoms of a life- threatening nature. The cause of death (neurologic versus systemic) will be determined from the medical records, available imaging studies, death certificate, and autopsy report (if available). At the expected accrual rate of 25 patients per arm per year, the neurologic death safety rule is expected to be evaluated just slightly over 2 years into the study, maximum (assuming that the 27th SRS patient needs to be followed for 1 year to trigger the rule). This rule, based on the exact binomial, has a one-sided type I error of less than 10% and greater than 81% power to detect a doubling of the 1-year neurologic death rate (from 18% to 36%).

11.5 Analysis of Primary Endpoints

Specified above

11.6 Analysis of Secondary Endpoints

Specified above

11.7 Reporting and Exclusions

All patients will be analyzed for all primary and secondary endpoints listed above based on the intent-to-treat principle.

11.7.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment. We will monitor for the following:

Fatigue

Fatigue is common after WBRT; it is less common and typically short-lived after stereotactic radiation but can still occur.



Nausea

Nausea is common with WBRT; it is less common with stereotactic radiation.

Headache

Headache that occurs with WBRT or stereotactic radiation is typically mild in severity.

Symptomatic edema

Symptomatic edema occurs when radiation interacts with the tumor, leading to death of tumor cells and resulting inflammation. It is more common with stereotactic radiation, particularly when given in a single fraction.

Seizure

Seizures are very rare with WBRT and occur in a small percentage of patients treated with stereotactic radiation.[21] Seizures generally do not stem from infratentorial lesions, however. Accordingly, for patients with supratentorial tumors being treated with stereotactic radiation in a single day, consideration of prophylactic levetiracetam 500 mg BID (or similar agent) will be used for 7 days (days 6 and 7 will entail only 500 mg daily of levetiracetam), with day 3 being the treatment day, at the discretion of the treating clinician.

Intracranial hemorrhage

Intracranial hemorrhage has never been definitively associated with radiation, although patients with tumors with a propensity to bleed (e.g. melanoma, renal cell, ovarian, thyroid) may display hemorrhage post radiation, especially if patients are on anticoagulation for other reasons. Intratumoral hemorrhage will require only close monitoring with MRI. Extratumoral hemorrhage may require referral to Neuro-oncology, admission, a treatment break, and possible discontinuation of agents that predispose to bleeding, depending on the nature and severity of the bleed.

Radiation necrosis

Radiation necrosis is rare after WBRT but can occur after stereotactic radiation. The most reliable predictor of radiation necrosis appears to be the volume of radiation receiving 12 Gy or more in a single treatment.[22,23] Enhancing lesions that increase in size after radiosurgery will be evaluated for the possibility of radiation necrosis using a dual-phase PET scan versus surveillance MRIs, at the discretion of the primary investigator.[24] Asymptomatic radiation necrosis will be monitored on brain MRI. Symptomatic necrosis will initially be managed with a brief (e.g. three week) course of dexamethasone. If refractory, referral to Neuro-oncology for consideration of bevacizumab[25] and neurosurgery for consideration of resection will be arranged.



Neurocognitive decline

Neurocognitive decline after WBRT is a commonly reported phenomenon.[12] The severity of neurocognitive dysfunction after WBRT varies significantly from patient to patient. Unfortunately, neurocognitive impairment is often irreversible. Memantine may minimize the impact of neurocognitive decline in patients receiving WBRT[26] and patients in our study who receive WBRT will be advised to use memantine as follows (with week 1 commencing with the first day of WBRT):

Week 1: 5mg qPM
Week 2: 5mg BID
Week 3: 5mg qAM and 10mg qPM
Week 4-24: 10mg BID

Patients who are tolerating memantine well will be offered to continue the drug beyond week 24 if deemed appropriate by the treating clinician.

12. REGULATORY CONSIDERATIONS

12.1 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.2 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix C.

13. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of



the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.



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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B SURVEY M. D. ANDERSON SYMPTOM INVENTORY – BRAIN TUMOR



Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

MD Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking (finding the words)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern (diarrhea or constipation)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

APPENDIX C DATA SAFETY MONITORING PLAN

DFCI IRB Protocol #: 16-305

APPENDIX C

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan



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1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.
Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC



Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Ayal Aizer, MD, MHS, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.



- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).



- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the



Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.



3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and e-mailed to the Coordinating Center **Clinical Research Coordinator, Rachel Brigell, at** rbrigell@partners.org:

- Signed informed consent document
- Completed Eligibility Checklist
- HIPAA Authorization Form (if applicable)

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).



- Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and assigned treatment arm.

Treatment or other protocol-specific interventions may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these



requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical



examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 6.1.9.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC CTRIO provides a web based training for all eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the



case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1 Ongoing Monitoring of Protocol Compliance

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of radiation plans, regulatory files, protocol departures reporting, and data management.

Participating institutions will be required to participate in monthly Coordinating Center initiated teleconferences. Participating Institutions will also be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification. Radiation plans, cause of death, and the primary endpoint (MDASI-BT) will be actively monitored by the Coordinating Center as outlined below. The DSMB will monitor all other aspects of the research.

4.1.1 Radiation Plans

In order to be eligible to treat patients on this study, physicians must be credentialed for contouring and treatment planning for hippocampal sparing WBRT and stereotactic radiation. Separate credentialing will be utilized for hippocampal sparing WBRT versus stereotactic radiation. All radiation oncologists at an institution participating in the study may enroll patients, but patients cannot be treated until the treating physician is credentialed for the particular modality of treatment that the patient has been randomized to. The credentialing process will entail a review of the contours and radiation plan for the first enrolled case for a given radiation modality, prior to treatment, by the principal investigator, Dr. Ayal Aizer, and the physics chair, Dr. Fred Hacker, or their designee. If no significant edits to the contours are indicated and if all planning criteria listed below are met the treating physician will be credentialed for that modality of radiation. Contours/plans which require significant adjustments by the principal investigator or physics chair must be edited prior to treatment initiation; in such cases, the physician seeking credentialing will be provided with feedback and must submit a contour/plan for review prior to treatment of the next patient enrolled and randomized to the particular modality of radiation being utilized.



4.1.2 Neurologic Death

The protocol contains an early stopping rule such that if 8 of the first 27 patients randomized to the stereotactic arm experience neurologic death prior to one year, the study will halt for re-evaluation of the safety of this regimen. Accordingly, if any of the first 27 patients assigned to the stereotactic arm who is registered at a Participating Institution dies within one year of radiation, both the local treating Radiation Oncologist at the Participating Institution and the DF/HCC Sponsor will separately determine whether the death is considered a neurologic death. If the two determinations are in accordance, the death will be ruled accordingly. If the determinations of the Participating Institution Radiation Oncologist and the DF/HCC Sponsor differ, a third study team member will be asked to contribute their determination.

4.1.3 MDASI-BT

The Coordinating Center will ensure compliance with the instrument used for the primary endpoint (MDASI-BT). Whenever the MDASI-BT is collected, a copy will be sent to the Coordinating Center. Every six months, the Coordinating Center will check in with Participating Institutions to ensure that the MDASI-BT has been collected for each study visit for each patient.

4.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

5. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

5.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-



day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

5.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

5.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

5.4 Participating Institution Performance

The DF/HCC Sponsor and the DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

