NRG ONCOLOGY

NRG-BN009

(ClinicalTrials.gov Identifier NCT #04588246)

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

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NRG-BN009: PHASE III TRIAL OF STEREOTACTIC RADIOSURGERY (SRS) OR HIPPOCAMPAL-AVOIDANT WHOLE BRAIN RADIOTHERAPY (HA-WBRT) FOR DISTANT BRAIN RELAPSE WITH BRAIN METASTASIS VELOCITY ≥4 BRAIN METASTASES/YEAR

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CONTACT INFORMATION (06-APR-2023)		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at http://www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance, or CTSURegHelp@coccg.org.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user logging on with CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		

For clinical questions (i.e., patient eligibility or treatment-related) Contact the study data manager listed on the NRG Oncology contact information table on the protocol cover page.
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
For imaging data submission questions: IROCimagearchive@acr.org; please include trial number in the email subject line **For TRIAD access and installation support:** TRIAD-Support@acr.org Triadhelp.acr.org **TRIAD Software Installation:** https://triadinstall.acr.org/triadclient/

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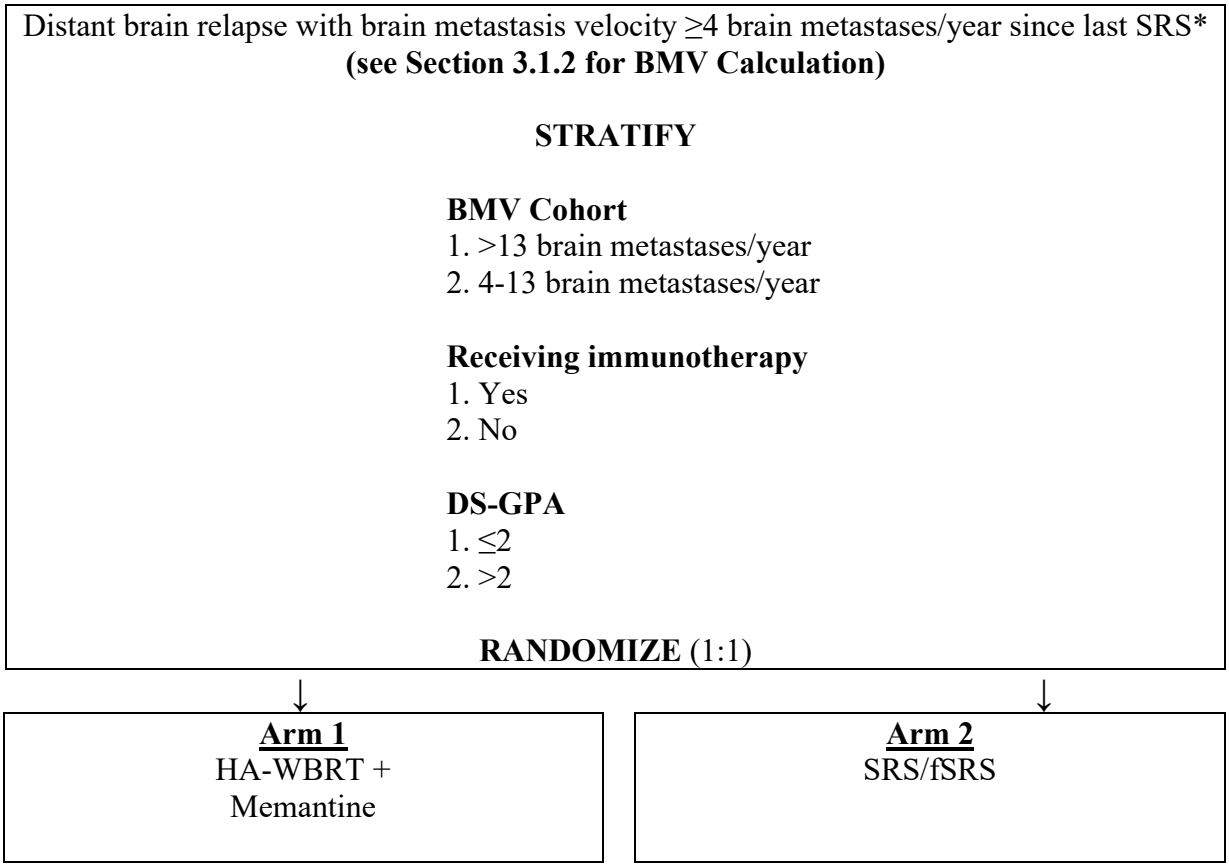
SCHEMA (06-APR-2023)



BMV = brain metastasis velocity; DS-GPA = diagnosis-specific graded prognostic assessment; fSRS = fractionated stereotactic radiosurgery; HA-WBRT = whole brain radiotherapy with hippocampal avoidance; SRS = stereotactic radiosurgery.

*See Appendix V. "Last SRS" refers to the most recent SRS procedure that the patient received prior to enrollment on this study.

1. OBJECTIVES

1.1 Primary Objective (06-APR-2023)

To determine if hippocampal-avoidant whole brain radiotherapy (HA-WBRT) in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year prolongs time to neurologic death as compared to stereotactic radiosurgery (SRS).

1.2 Secondary Objectives (06-APR-2023)

1.2.1 To determine if HA-WBRT in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year prolongs overall survival as compared to SRS.

1.2.2 To evaluate if HA-WBRT in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year prolongs intracranial progression-free survival as compared to SRS.

~~1.2.3~~1.1.3 To evaluate if HA-WBRT in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year improves brain metastasis velocity at subsequent relapse as compared to SRS.

1.2.4 To assess perceived difficulties in cognitive abilities, symptom burden and health status after HA-WBRT, as compared to SRS, in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year.

1.2.5 To compare neurocognitive function outcomes following HA-WBRT, as compared to SRS, in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year.

1.2.6 To tabulate and descriptively compare the adverse events associated with the interventions

1.2.7 To tabulate and descriptively compare the number of salvage procedures used to manage recurrent intracranial disease following the interventions

1.3 Exploratory Objectives (06-APR-2023)

1.3.1 To collect serum, plasma, and whole blood for translational research analyses.

1.3.2 To collect baseline and all follow-up MR imaging for hippocampal volume, memory center substructures, Axial T2 volumes, and quantitative texture analysis.

1.3.3 To collect baseline and follow-up MR imaging to extract whole brain volume, white matter volume and volume of metastatic disease to correlate with cognitive change at 4 months.

1.3.4 To evaluate dose-volume histogram parameters to correlate with radiation toxicity.

1.3.5 To assess in patients receiving immunotherapy or targeted therapy, if HA-WBRT in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year at time improves brain metastasis velocity and/or overall survival at subsequent relapse as compared to SRS.

1.3.6 To compare the estimated cost of brain-related therapies and quality-adjusted life years in patients who receive HA-WBRT, as compared to SRS, in patients with distant brain failure with metastasis velocity ≥4 new brain metastases/year.

2. BACKGROUND

2.1 Choice of Salvage Therapy: Whole-Brain Radiotherapy versus Stereotactic Radiosurgery (06-APR-2023)

The development of brain metastases is an unfortunate and common complication in oncology patients and can occur in 10% to 30% of cancer patients (Brown 2018). Stereotactic radiosurgery (SRS) has replaced WBRT as standard upfront therapy for patients with four or fewer brain metastases due to improved cognitive and patient-reported outcomes (Brown 2016; Chang 2009; Soffietti 2013). Multiple phase III randomized trials have now shown that WBRT does not improve survival compared to SRS alone in patients with 4 or fewer brain metastases (Kocher 2010; Aoyama 2006; Churilla 2017). Results from a recent Japanese phase II study suggest that SRS is also feasible in patients with up to 10 brain metastases (Yamamoto 2014), and the application of SRS in the setting of multiple (>4) brain metastases continues to increase.

The expanding application of SRS has led to an increasing incidence of distant brain relapses that represent untreated micro-metastatic disease, which would have been traditionally treated with upfront WBRT. In the setting of 1-4 newly diagnosed brain metastases, this inferior intracranial control of SRS has not translated into decrements in survival, cognition or patient-reported outcomes. However, recent evidence suggests that the cognitive decline seen in patients with SRS, while less than with WBRT, can still be significant (Brown 2016). What is not known is whether multiple serial salvage SRS procedures may collectively worsen cognition or quality of life. This question has not been studied in the setting of distant brain relapse after SRS, where there exists a paucity of data to guide salvage therapy decisions.

The use of WBRT has shown superior intracranial control over SRS monotherapy in published randomized trials (Brown 2016, Kocher 2011, Aoyama 2006, Andrews 2004), given the higher distant brain failure following SRS (Brown 2016, Kocher 2011, Aoyama 2006). Given that the cumulative effects of distant brain failures can lead to neurologic deterioration, a WBRT approach is the modality likely best able to mitigate neurologic deterioration in the setting of more extensive brain metastasis relapse.

2.2 Brain Metastasis Velocity (06-APR-2023)

The research team at Wake Forest University published on the concept of brain metastasis velocity (BMV) at the time of distant brain relapse after SRS. This metric has the capacity to predict the risk of developing serial distant brain relapses after salvage SRS and is strongly associated with survival and neurologic death (Farris 2017). BMV is defined as:

$$\text{Brain metastasis velocity (BMV)} = \frac{\text{[Total number of new brain metastases since last SRS]}}{\text{[Time interval (in years) since upfront SRS]}}$$

In a cohort of 737 brain metastasis patients from a single institution, Farris et al. observed that BMV at first or second distant brain relapse after SRS predicted for

overall survival (Figure 1a) (Farris 2017). In a larger validation dataset of >2000 brain metastasis patients from 9 other institutions, BMV remained prognostic with nearly identical median survival outcomes (Figure 1b) (McTyre 2017). Specifically, patients who had a BMV≥4 brain metastases/year had a 7-month shortening in median survival as compared to patients with BMV<4 brain metastases/year (p<0.0001). Interestingly, the prognostic capacity of BMV remained significant over multiple different systemic therapy eras (i.e., before or after 2007, roughly correlating with the emergence of multiple targeted therapies with brain penetration). BMV at first distant brain relapse was also predictive of BMV at second distant brain relapse, highlighting the ability of BMV to serve as a surrogate marker for intracranial control. The prognostic value of BMV has since been validated in two additional published series (Figure 1c) (Yamamoto 2019, Fritz 2018).

Importantly, using a centralized definition of neurologic death, BMV at first or second distant brain relapse after SRS predicted for neurologic death following salvage SRS (Figure 2) (Fritz 2018). In this study, neurologic death was defined as progressive neurologic decline at time of death irrespective of status of extracranial disease or death from inter-current disease in patients with severe neurologic dysfunction (Table 1). Patients with BMV≥4 brain metastases/year were nearly 2-fold more likely to suffer neurologic death than patients with BMV<4 brain metastases/year. A recent analysis of brain metastasis patients treated with SRS in the immunotherapy era confirmed that BMV remained prognostic for both overall survival and neurologic death, with >7-fold increased risk of neurologic death in patients with BMV≥4 brain metastases/year (p=0.005) (Figure 2b) (LeCompte 2019).

The summation of these findings underscores the capacity of BMV following SRS to distinguish a subset of patients (BMV≥4 brain metastases/year) whose inferior intracranial control with salvage SRS significantly raises the risk of neurologic death as a primary contributor to inferior survival. Thus, prevention of neurologic death in this high-risk population is an important treatment goal that may impact overall survival, especially as systemic therapies continue to improve control of extracranial disease.

Figure 1

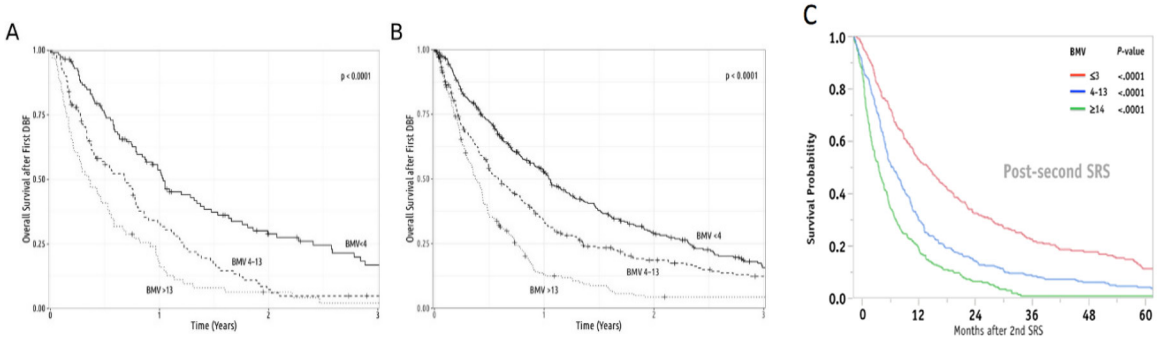
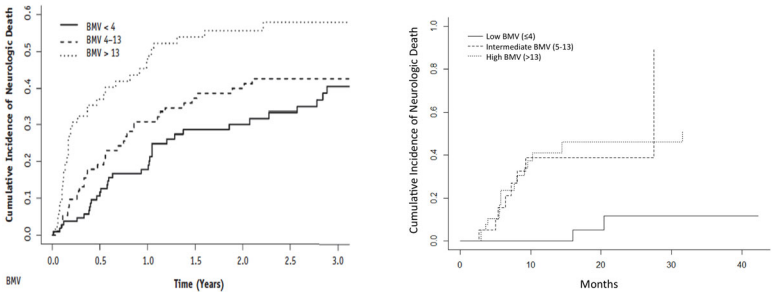


Figure 2

A **B**



2.3 Neuroprotective Strategies During WBRT (06-APR-2023)

Studies demonstrating inferior cognitive outcomes following WBRT relative to SRS for 1-4 brain metastases were largely conducted prior to the publication of large brain metastasis trials testing pharmacologic and technologic neuroprotective strategies during WBRT. These trials were conducted through the legacy RTOG/NRG Oncology cooperative groups and have significantly advanced our approach to safer delivery of WBRT.

RTOG 0614 was a phase III trial of prophylactic memantine versus placebo during WBRT for patients with brain metastases (Brown 2013). In this trial of 554 patients, the addition of memantine to WBRT significantly prevented cognitive decline (HR 0.78; 95% CI, 0.62 to 0.99; p=0.02) (Figure 3A). These practice-changing results led to the establishment of prophylactic memantine as standard of care during WBRT.

RTOG 0933 was a phase II trial of conformal avoidance of the hippocampus during WBRT using intensity-modulated radiotherapy for patients with brain metastases (Gondi 2015). This trial demonstrated highly promising cognitive outcomes relative to historical controls and served as the basis for NRG-CC001, a phase III trial of WBRT with memantine with or without hippocampal avoidance during WBRT for patients with brain metastases. NRG-CC001 reached its target accrual in March 2018 with 518 patients randomized. There was no difference in grade 3 or higher toxicity between the treatment arms. The median follow-up for alive patients was 7.8 months. There was no difference between arms in terms of baseline cognitive function, overall survival (HR=1.13, 95% CI: 0.89-1.44, p=0.31) or intracranial progression (HR 1.12, 95% CI 0.90-1.39, p=0.33).

The addition of hippocampal avoidance to WBRT plus memantine significantly prevented cognitive decline (Figure 3B; adjusted HR=0.74, 95% confidence interval (CI): 0.58-0.95, p=0.02) (18). The difference was first seen at 4 months and maintained throughout the follow-up period, and was attributable to improvements in executive function at 4 months (p=0.01) and learning (p=0.049) and memory (p=0.02) at 6 months. While age also predicted for prevention of cognitive function failure, test for interaction between treatment arm and age was non-significant (p=0.67), indicating that the cognitive benefit of hippocampal avoidance does not differ by age.

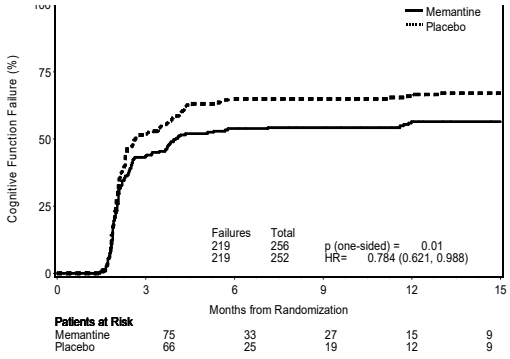
Importantly, the addition of hippocampal avoidance to WBRT+memantine preserved patient-reported symptom burden, as assessed by the M.D. Anderson Symptom

Inventory Brain Tumor Module (MDASI-BT). Patients on the HA-WBRT+memantine arm experienced less symptom interference and less cognitive symptoms at 6 months (estimate=-1.02, p=0.008 and estimate=-0.63, p=0.011, respectively, Table 5) compared to the WBRT+memantine arm. Cognitive symptom differences were driven primarily by 2 items: problems with remembering things and difficulty speaking. At 6 months, patients on the HA-WBRT+memantine arm had less difficulty remembering things (mean 0.16 vs. 1.29, p=0.013) and less difficulty speaking (mean -0.20 vs. 0.45, p=0.049) as compared to the WBRT+memantine arm. Greater improvement in fatigue at 6 months was reported in the HA-WBRT+memantine arm as compared to the WBRT+memantine arm (mean 0.93 vs. -0.16, p=0.036). Analyses with longer follow-up (median follow-up of 12.1 months) additionally demonstrated better preservation of overall symptom burden (p<0.0001) at 6 months on the HA-WBRT+memantine arm compared to the WBRT+memantine arm, while continuing to show similar benefits in cognitive function and patient-reported quality of life with hippocampal avoidance.

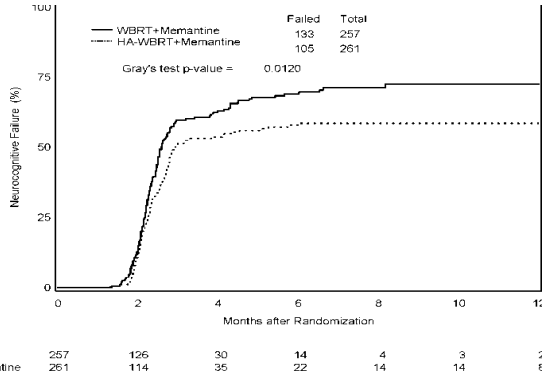
Based on these practice-changing results, the WBRT arm on this proposed phase III trial will include both neuroprotective strategies of prophylactic memantine and hippocampal avoidance using intensity-modulated radiotherapy. Importantly, this trial will be one of a few ongoing studies of SRS versus WBRT to incorporate both highly effective neuroprotective strategies on the WBRT arm in a manner that will compare the neurocognitive and patient-reported cognitive and quality of life effects of greater intracranial control versus more targeted intracranial treatment in the modern management of brain metastases. Thus, for this trial, neurocognitive function (NCF) and patient-reported outcomes (PRO) will be included as important secondary endpoints to compare both neurocognitive outcomes, as well as the perceived impact of cognitive symptoms on function, overall symptom burden and general health status.

Figure 3

A



B



2.4 Neurocognitive Function and Patient Reported Outcomes

The current trial will build on the successes of RTOG 0614 and NRG-CC001 in utilizing the same NCF and PRO measures with the addition of the PROMIS Cognitive Function Short Form 4a self-report assessment. There are a number of advantages of such an approach including familiarity and acceptance of these measures by clinical

research staff, the well-established use and validation of these measures in brain metastasis research, and the possibility of future post-hoc analyses between studies.

The neurocognitive tests to be used in this study (the Hopkins Verbal Learning Test – Revised (Benedict 1998), Trail Making Test (Tombaugh 2004), and the Controlled Oral Word Association (Ruff 1996) are the same tests as were used in RTOG 0614, NRG-CC001, NCCTG/Alliance N0574, and NCCTG/Alliance N107C, and that are being used in numerous ongoing brain met trials (e.g., NRG-CC003, SWOG S1827).

While NCF outcomes have been recognized as being crucial in the brain metastasis population (Lin 2013), there is also interest in evaluating the impact of treatment arm on patient-reported outcomes. PROMIS Cognitive Function Short Form 4a measures perceived cognitive abilities (e.g., memory, attention, and decision making) and the application of such abilities to everyday tasks (e.g., planning, organizing, calculating, remembering and learning). Symptom assessment measures such as the MDASI-BT have been specifically developed in patients with brain tumors to capture patient self-reports of symptom severity and the patient's perception of the impact or interference with daily activities. The MDASI-BT has demonstrated reliability and validity in the brain tumor patient population, including predictive validity for tumor recurrence (Armstrong 2006, Armstrong 2011) and sensitivity to cognitive preservation strategies (Brown in press). Health-related general health status will also be measured using the EQ-5D-5L, an established, validated measure that has been used in brain metastasis populations (Takura 2010, Langley 2013). Combined, the PROMIS, MDASI-BT and EQ-5D-5L assessments are brief and therefore not a significant burden for patients to complete.

2.5 Economic and Comparative Effectiveness Analysis (06-APR-2023)

Prior cost-effectiveness analysis (CEA) studies of SRS for brain metastases have been focused on patients with newly diagnosed brain metastases (Lester-Coll 2016), and have typically not accounted for increased costs of WBRT with hippocampal avoidance and memantine (Savitz 2015). This will be the first study to prospectively conduct a CEA of SRS and HA-WBRT with memantine for patients requiring salvage brain-directed radiotherapy for recurrent brain metastases.

2.6 MR Imaging Analyses (06-APR-2023)

Imaging-based predictors of neurocognitive decline are becoming increasingly informative for clinicians making decisions for their patients with brain metastases. Prior work has shown that MR T2/FLAIR volume significantly increases after WBRT and that the presence of pre-treatment MR T2/FLAIR abnormality is a predictor of white matter injury (WMI) post-treatment (Sabsevitz 2013). Furthermore, on secondary analysis of RTOG 0933, pre-treatment MR T2/FLAIR WMI was found to correlate with subsequent memory decline following HA-WBRT (Bovi 2019). This observation was corroborated on planned NRG CC001 secondary analysis, which demonstrated that pre-treatment WMI volume predicted for post-treatment neurocognitive decline at 4- and 12-months following HA-WBRT (Bovi 2020). These findings suggest a greater baseline susceptibility to neurocognitive decline in patients with larger volume pre-

treatment despite attention to hippocampal dosimetry. As a follow-up to these findings, we hypothesize that brain metastasis patients with larger MR-determined pre-treatment WMI develop more neurocognitive decline.

In addition to WMI, WBRT can lead to atrophy of the brain and various substructures including the hippocampus (Hoffmann 2018, Seibert 2017). Additional studies have also found a correlation with whole brain volume loss, poor cognition, and overall survival (Gui 2019, Hoffman 2018). Injury to the right versus left hippocampus appears to correlate with loss of different memory outcomes. Pediatric patients demonstrate worse visual and memory outcomes with radiation when there is higher dose to the left hippocampus (Zureick 2018). In healthy older adults, hippocampal volumes correlate with episodic memory (Caillaud 2019). An additional hypothesis is that the use of HA-WBRT in lieu of SRS may lead to more atrophy of the whole brain and hippocampus, correlating with inferior cognitive outcomes. The volume of the whole brain and memory substructures will be measured in NRG-BN009 to enable future explorations of these objectives.

2.7 Summary (06-APR-2023)

At the present time, no level I evidence exists on appropriate salvage therapy (SRS or HA-WBRT) for distant brain relapses after SRS management. As such, there is no established standard of care in this important and increasingly common real-world scenario. BMV following SRS distinguishes a subset of patients (BMV≥4 brain metastases/year) whose inferior intracranial control with salvage SRS not just portends poorer survival, but also significantly raises the risk of neurologic death as a primary contributor to that survival. Improving intracranial control in this high-risk population is an important treatment goal in order to prevent neurologic death. Given the predominance of neurologic causes for death in this high-risk population and ongoing improvements in systemic therapy for control of extracranial disease, prevention of neurologic death may also impact overall survival.

We hypothesize that for patients with distant brain failure with BMV ≥4 brain metastases/year, the improved intracranial control of HA-WBRT relative to SRS will translate into benefits in terms of prevention of neurologic death and, as a secondary endpoint, prolongation of overall survival. Given practice-changing advances in the use of prophylactic memantine and hippocampal avoidance as neuroprotective strategies to enable safer delivery of HA-WBRT, as secondary objectives, we seek to also compare the NCF and patient-reported outcomes of HA-WBRT relative to SRS.

Demonstration of neurologic death and overall survival benefits from HA-WBRT for patients with distant brain failure with BMV ≥4 brain metastases/year would not only validate the importance of BMV as a predictor of survival outcomes, but also establish a role for HA-WBRT in the management of such high-risk brain metastasis patients. Any associated survival benefit of HA-WBRT over SRS would have to be weighed against any corresponding impact on patient-reported cognitive, symptom or quality of life outcomes, which are important patient-centered outcomes that will be prospectively and longitudinally collected in this proposed study. If this proposed trial were not to

find a neurologic death or overall survival benefit from HA-WBRT, then the secondary endpoint of patient-reported outcomes would help define the appropriate salvage therapy, especially given the inclusion of practice-changing neuroprotective strategies of prophylactic memantine and hippocampal avoidance during WBRT.

Additionally, the question of whether SRS or HA-WBRT is the optimal salvage modality for distant brain relapse is significant from a medical resources standpoint, given high costs of both treatment approaches at a time of increasing emphasis on value-based healthcare delivery. Given the growing support by patients and healthcare providers for multiple serial SRS treatments (over an HA-WBRT approach that may obviate the need for subsequent SRS treatments due to improved intracranial control) without well-established risk/benefit data, there is a critical need for a robust cost-effectiveness analysis of both treatment approaches in the setting of a prospective multi-institutional cooperative group clinical trial. Thus, this trial includes proposed comparative and cost-effectiveness secondary analyses.

Finally, in the contemporary era where many patients with brain metastases receive treatment prior to or after their distant brain relapse with either targeted therapies or immunotherapies, there is a need for a clearer understanding of both the potential toxicities as well as potential benefits of these treatments in relation to HA-WBRT versus SRS. While the advent of immunotherapies has improved survival outcomes in subgroups of brain metastasis patients, neurologic death remains a relevant endpoint. Two recent analyses have assessed the effect of immunotherapies on neurologic death in the brain metastasis population. Lanier et al (2019) reported a cumulative incidence of neurologic death in brain metastasis patients receiving immunotherapy was only 10%. However, in the population with BMV ≥4 brain metastases/year, LeCompte et al (2019) reported cumulative incidence of neurologic death to be 38%, confirming in a modern immunotherapy-treated population that neurologic death rates remain unacceptably high in the BMV≥4 cohort. This prospective study with pre-specified endpoints addressing these issues and including immunotherapy usage as a stratification factor will provide additional insight.

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Notes: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Statistics and Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the

recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf

3.1. Eligibility Criteria (06-APR-2023)
A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 Patients must have developed their distant brain relapse(s) at least 8 weeks after last SRS and within 21 days prior to randomization

- Distant brain relapse lesions to be treated must measure ≤3.0 cm in maximal extent and total volume of distant brain relapses to be treated must measure <30 mL on the contrast-enhanced diagnostic MRI brain scan obtained within 21 days prior to randomization.
- "last SRS" refers to the most recent SRS procedure that the patient received prior to enrollment on this study.
- Distant brain relapse lesions must be diagnosed on MRI, which will include the following elements:

REQUIRED MRI ELEMENTS

- Post gadolinium contrast-enhanced T1-weighted three-dimensional (3D) spoiled gradient (SPGR). Acceptable 3D SPGR sequences include magnetization-prepared 3D gradient recalled echo (GRE) rapid gradient echo (MP-RAGE), turbo field echo (TFE) MRI, BRAVO (Brain Volume Imaging) or 3D Fast FE (field echo). The T1-weighted 3D scan should use the smallest possible axial slice thickness, not to exceed 1.5 mm.
- Pre-contrast T1 weighted imaging (3D imaging sequence strongly encouraged).
- A minimum of one axial T2 FLAIR (preferred) or T2 sequence is required. This can be acquired as a 2D or 3D image. If 2D, the images should be obtained in the axial plane.

ADDITIONAL RECOMMENDATIONS

- Recommendation is that an axial T2 FLAIR (preferred) sequence be performed instead of a T2 sequence.
- Recommendation is that that pre-contrast 3D T1 be performed with the same parameters as the post-contrast 3D T1.
- Recommendation is that imaging be performed on a 3 Tesla (3T) MRI.
- Recommendation is that the study participants be scanned on the same MRI instrument at each time point.
- Recommendation is that if additional sequences are obtained, these should meet the criteria outlined in Kaufmann et al., 2020.
- If additional sequences are obtained, total imaging time should not exceed 60 minutes.

See Appendix IV for a summary of key imaging requirements, and contact the Neuroradiology and Imaging Co-Chairs for further information or assistance if needed.

3.1.2 Brain metastasis velocity (BMV) since last SRS must be ≥4 brain metastases/year.

Use the following equation to calculate BMV

$$\text{BMV} = \frac{\text{[Total number of new brain metastases since last SRS]}}{\text{[Time interval (in years) since last SRS]}}$$

"last SRS" refers to the most recent SRS procedure that the patient received prior to enrollment on this study.

BMV calculations should be **rounded down** to integers. **For example**, a patient who had the last SRS 2.6 years ago and had 10 (cumulative) new brain metastases since then would have BMV = 10/2.6 = 3.85. This patient would be assigned to the BMV < 4 category, and hence is NOT eligible for this trial.

3.1.3 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.1.4 Pathologically (histologically or cytologically) proven diagnosis of small cell cancer, non-small cell lung cancer, melanoma, breast cancer, renal cell carcinoma, or gastrointestinal cancer within 10 years prior to randomization. If the original histologic proof of malignancy is greater than 10 years, then pathological (i.e., more recent) confirmation is required (e.g., from a systemic metastasis or brain metastasis).

- Other histologies are not permitted.

3.1.5 History and physical examination within 28 days prior to randomization

3.1.6 Age ≥ 18

3.1.7 Karnofsky Performance Status of ≥70 within 28 days prior to randomization;

3.1.8 Adequate renal function within 28 days prior to randomization defined as follows:

- Calculated creatinine clearance (CrCl) ≥30 ml/min
  For males: CrCl = [140-age (years)] · *Weight (kg)/[72 · serum creatinine (mg/dL)]
  For females: CrCl = 0.85 · [140-age (years)] · *Weight (kg)/[72 · serum creatinine (mg/dL)]
  *Actual weight should be used unless patient is greater than 30% above IBW, then used Adjusted BW (= IBW + 0.4*actual BW) in the Cockcroft Gault equation.
- BUN within 1.5 times the institutional upper limit of normal (ULN) (e.g., if the ULN is 20 mg/dL, then BUN up to 30 mg/dL is permitted).

3.1.9 Negative urine or serum pregnancy test (in women of childbearing potential) within 14 days prior to randomization.

3.2 Ineligibility Criteria (06-APR-2023)
Patients with any of the following conditions are NOT eligible for this study.

3.2.1 BMV ≥4 brain metastases/year at time of any SRS prior to enrollment.
- Patients are permitted to have undergone multiple SRS treatments to different brain metastases so long as prior BMV has been less than 4 brain metastases/year.

3.2.2 Prior WBRT or prophylactic cranial irradiation.

3.2.3 Local relapse of metastasis previously treated with upfront SRS (i.e., relapse outside previously SRS-treated metastases is allowed)

3.2.4 Brain metastases from primary germ cell tumor or lymphoma.

3.2.5 Definitive leptomeningeal metastasis.

3.2.6 Planned cytotoxic chemotherapy on the same day as SRS or HA-WBRT; Concurrent immunotherapy is permitted.

3.2.7 Radiographic evidence of enlargement or other architectural distortion of the lateral ventricles, including placement of external ventricular drain or ventriculoperitoneal shunt.

3.2.8 Known history of demyelinating disease such as multiple sclerosis

3.2.9 Inability to swallow pills

3.2.10 Contraindication to MR imaging such as non-MR conditional implanted metal devices or unknown metallic foreign bodies, or contraindication to gadolinium contrast administration during MR imaging, such as anaphylactic allergy that cannot be adequately addressed with pre-contrast medications or acute kidney injury

3.2.11 Contraindications to memantine, including:
- Allergy, including prior allergic reaction to memantine
- Intractable seizures on adequate anticonvulsive therapy—more than 1 seizure per month for the past 2 months
- Current use of NMDA agonist
- Current alcohol or drug abuse, which can exacerbate lethargy/dizziness with memantine

3.2.12 Severe, active co-morbidity defined as follows:
- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of randomization
- Chronic obstructive pulmonary disease exacerbation or other acute respiratory illness precluding study therapy at the time of randomization
- Severe hepatic disease defined as a diagnosis of Child-Pugh class B or C hepatic disease
- Renal tubular acidosis or metabolic acidosis
- HIV positive with CD4 count < 200 cells/microliter. Note that patients who are HIV positive are eligible, provided they are under treatment with highly active antiretroviral therapy (HAART) and have a CD4 count ≥ 200 cells/microliter within 30 days prior to randomization. Note also that HIV testing is not required for eligibility for this protocol.

3.2.13 Pregnant or lactating women, or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the medication and radiation involved in this study has unknown effects on the unborn fetus.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

(06-APR-2023)

PRE-TREATMENT ASSESSMENTS

Assessment	Prior to Randomization	Prior to Treatment
Brain MRI w/wo contrast (See Section 3.1.1 and Appendix IV) demonstrating BMV≥4 brain metastases/year since last distant brain relapse	Within 21 days	
Neurocognitive: HVLT-R, TMT, COWA (upload in RAVE required)		X
QOL: MDASI-BT, EQ-5D-5L, PROMIS cognitive function*		X
Histological/cytological evaluation	X	
Neurologic exam*	Within 28 days	
History/physical exam*	Within 28 days	
Karnofsky performance status*	Within 28 days	
Calculated creatinine clearance, BUN	Within 28 days	
Urine or serum pregnancy test *(if applicable)*	Within 14 days	
Serum for banking and laboratory correlative studies (for consenting patients; see Section 10 for details)		X

*In person preferred; may be conducted by telehealth visit at the discretion of the site-identified qualified healthcare professional.

ASSESSMENTS DURING TREATMENT AND IN FOLLOW-UP

Assessments	**From start of SRS/fSRS or HA-WBRT: at months 2, 4, 6, 9 and 12** (+/- 2 weeks)	**Every 6 months after month 12** (+/- 4 weeks)	**Within 21 days after patient death**
Physical exam*	X	X	
Neurologic exam*	X	X	
Karnofsky performance status*	X	X	
Adverse event evaluation	X	X	
Calculated creatinine clearance (Arm 1 patients)	At each visit while on memantine, or as clinically indicated.		
Brain MRI w/wo contrast (See Section 3.1.1 and Appendix IV)	X	As clinically indicated	
Neurocognitive: HVLT-R, COWA, TMT (upload in RAVE required)	X		
QOL: MDASI-BT, EQ-5D-5L, PROMIS cognitive function*	X		
Serum for banking and laboratory correlative studies (for consenting patients; see Section 10 for details)	Within 2 months of start of SRS/fSRS or HA-WBRT		
Assessment of neurologic death (for details, see Definition of Disease Assessments/ Neurologic Death) below			X

*In person preferred; may be conducted by telehealth visit at the discretion of the site-identified qualified healthcare professional.

Definition of Disease Assessments

Neurologic death:

Within 21 days of patient death, the Neurologic Death Form should be completed by the

treating physician to determine if death was due to neurologic causes and submitted via Medidata Rave. In addition, any medical record documentation that supports this assessment should be submitted via Medidata Rave to facilitate central review of neurologic death assessment. All submitted medical record documentation should have all Protected Health Information (PHI) blacked out.

Each Neurologic Death Form will undergo real-time central review by the trial's Co-Principal Investigators Dr. Gondi and Dr. Chan and Neuro-Oncology Co-Chair Dr. Lukas, all of whom will be blinded to the treatment arm of the enrolled patient.

Definition of neurologic death (death due to neurologic causes):
1) Progressive neurologic decline or new neurologic symptoms/signs at time of death irrespective of status of extracranial disease OR
2) Death from inter-current disease in patients with severe neurologic dysfunction.

Sample of Case Report Form for Neurologic Death determination:
(Please note this is only a sample, is subject to change, and should be used only as a guide with precise details/information provided on the Case Report Form.)

Date of death:

1. Prior to death, was the patient experiencing progressive neurologic decline? (Y/N)
If Y, were they experiencing progressive
... motor weakness? (Y/N)
... difficulty with ambulation? (Y/N)
... vision changes? (Y/N)
... difficulty understanding? (Y/N)
... difficulty speaking? (Y/N)
... seizures? (Y/N)
... confusion? (Y/N)
... episodes of mental status changes? (Y/N)
... cognitive slowing? (Y/N)
…cranial nerve palsies? (Y/N)
... other neurologic symptoms (Y/N). If Y, please define.

2. One month prior to death, was the patient experiencing any new neurologic symptoms/signs? (Y/N)
If Y, were they experiencing new
... motor weakness? (Y/N)
... difficulty with ambulation? (Y/N)
... vision changes? (Y/N)
... difficulty understanding? (Y/N)
... difficulty speaking? (Y/N)
... seizures? (Y/N)
... confusion? (Y/N)
... episodes of mental status changes? (Y/N)
... cognitive slowing? (Y/N)
…cranial nerve palsies? (Y/N)
... other neurologic symptoms (Y/N). If Y, please define.

3. If Y to (1) or (2), did the patient develop other progressive medical conditions (e.g., hepatic encephalopathy) that could explain the progressive neurologic decline or new neurologic symptoms/signs? (Y/N)
If such a progressive medical condition existed, please define and explain the progressive medical condition and please provide information on the status of intracranial metastatic disease on last brain MRI before death.

4. If N to (1) or (2) and death is due to inter-current disease, did the patient have severe neurologic dysfunction at time of death? (Y/N). If Y, please define.

Intracranial progression

Target lesions: Contrast-enhancing lesions that can be accurately measured in at least one dimension with a minimum diameter being double the slice thickness of the MRI scan (0mm skip) and is visible on two or more axial slices (e.g.., the minimal lesion diameter can be 4mm if the slice thickness is 2mm with 0mm skip).
The diameter perpendicular to the longest diameter in the plane of measurement should be at least 2mm for the lesion.
Lesions around a cyst or surgical cavity should not be considered a target lesion unless there is a nodular component that measures 5mm or more in longest diameter and 2mm or more in perpendicular plane. The cystic or surgical cavity should not be measured for the determination of a response.

As per RANO-BM criteria (Lin 2015), intracranial progression will be defined as:

1) Local progression of lesions treated with prior radiation
    a. At least a 20% increase in the sum of longest diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) and
    b. At least a 5mm or more increase in one target lesion, or

2) Distant Progression/development of new brain lesion
    a. A new lesion is one that was not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow up assessment will determine if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of initial scan showing the new lesion.

Note: Intracranial leptomeningeal progression is a subtype of distant progression characterized by linear, curvilinear, or nodular contrast enhancement along the leptomeningeal surfaces including, but not limited, cortical sulci, cranial nerves, cerebellar folia, and ventricular ependymal surfaces. Cytological evaluation of cerebrospinal fluid (CSF) can offer confirmatory data on suspected leptomeningeal progression, but is not required for diagnosis. Questions regarding leptomeningeal progression in an individual case should be reviewed with the local Radiologist.

Brain metastasis velocity at subsequent distant brain relapse

Brain metastasis velocity at subsequent distant brain relapse (BMVs) is defined as follows:

$$\text{Brain metastasis velocity (BMVs)} = \frac{\text{[Total number of new brain metastases since on-study SRS/HA-WBRT]}}{\text{[Time interval (in years) since on-study SRS/HA-WBRT]}}$$

5. TREATMENT PLAN/REGIMEN DESCRIPTION (06-APR-2023)

Protocol treatment must begin within 21 calendar days after randomization and within 42 days of diagnostic MRI used for eligibility.

Protocol Treatment	Arm 1*	Arm 2	Dose
SRS/fSRS		**X**	See Section 5.2.
HA-WBRT	**X**		30 Gy in 10 fractions over 2 weeks
Memantine	**X**		Target BID dose 20 mg/day OR target extended-release dose 28 mg/day (refer to tables in 5.1.2)

***Arm 1:** At the treating physician's discretion, consolidative SRS boost to selected brain metastases following HA-WBRT is permitted during the follow-up period before radiographic progression of those brain metastases. There are no protocol specifications regarding this consolidative SRS boost.

5.1 Arm 1: Memantine (06-APR-2023)

5.1.1 Memantine should preferably start prior to HA-WBRT as soon as possible after randomization but must start no later than before the fourth HA-WBRT treatment.

If a patient is enrolled on the study and is unable to acquire memantine, the patient should remain on the study and otherwise proceed per the assigned treatment per study guidelines and be followed per protocol. This should be documented in the memantine pill diary.

5.1.2 Both extended release memantine and twice daily memantine dosing will be allowed. Patients continue on memantine for 24 weeks. The dosing and schedule will be outlined separately for each. See Section 6 for dose modifications in the setting of abnormal renal function.

Twice Daily Dosing Memantine

The target dose for memantine is 20 mg (10 mg divided twice daily). Dose is escalated by 5 mg per week to target of 10 mg twice daily (i.e., 5 mg a day for week 1, then 5 mg BID for week 2, then 10 mg in AM and 5 mg in PM for week 3, then 10 mg in AM and 10 mg in PM by week 4).

	Daily AM Dose	Daily PM Dose
Week 1	5 mg	None
Week 2	5 mg	5 mg
Week 3	10 mg	5 mg
Weeks 4-24	10 mg	10 mg

Extended Release Memantine

The target dose for extended release memantine is 28 mg. Dose is escalated by 7 mg

per week to target of 28 mg daily (i.e., 7 mg a day for week 1, then 14 mg a day for week 2, then 21 mg a day for week 3, then 28 mg a day for by week 4).

	Daily Dose Extended Release Memantine
Week 1	7 mg
Week 2	14 mg
Week 3	21 mg
Weeks 4-24	28 mg

Administration

Memantine is administered by mouth taken with full glass of water (>8 oz). Memantine is well absorbed after oral administration and absorption is not affected by food and therefore can be taken with or without food. Doses should be taken within 2 hours of scheduled time. For the twice daily dosing memantine, outside the 2 hours, patient should skip the dose. Missed doses should be documented but patients should not try to make up missed doses. If treatment is interrupted for longer than several days, dosing may need to be resumed at lower doses and retitrated. Memantine should be continued through the duration of 24 weeks regardless of disease status (i.e., if a patient progresses in the brain as long as study drug is tolerated study drug should be continued).

Memantine Pill Diary

Prior to starting treatment, the patient will be provided with and instructed in the proper use of a pill diary (See Appendix II) to record daily pill consumption. This record will be checked for compliance by the study nurse. The diary will be retained in the patient's record for submission to NRG ONLY upon request; i.e., diaries are not to be submitted but will be retained at the site as source documents. Compliance will be assessed by the study nurse at each study visit during treatment (at months 2, 4, and 6) and is defined as >85% of doses accurately taken, but for any noncompliance patients must be re-instructed. If treatment is interrupted for longer than several days, dosing may need to be resumed at lower doses and retitrated.

5.2 Radiation Therapy (06-APR-2023)

5.2.1 Arm 1: HA-WBRT

Pre-treatment reviews are required for both credentialed and non-credentialed physicians. The Pre-Treatment Review process requires 3 business days from the receipt of complete data.

PHYSICIANS/INSTITUTIONS PREVIOUSLY CREDENTIALED FOR HA-WBRT:

Patients can be enrolled by treating physicians and institutions that have passed pre-enrollment benchmark cases for hippocampal contouring and HA-WBRT treatment planning from prior or ongoing trials NRG-CC009, NRG-CC003, NRG-CC001, RTOG 0933, or CCTG CE.7.

The first patient enrolled from each credentialed treating physician and institution in Arm 1

will require a Pre-Treatment Review of hippocampal contouring and HA-WBRT treatment plan. Credentialed physicians and institutions and that have passed one (1) pre-treatment review of a patient enrolled on the HA-WBRT arm of NRG-CC009, NRG-CC003, NRG-CC001, or CCTG CE7 will be permitted to enroll patients on NRG-BN009 without pre-treatment case review.

The patient cannot start treatment until they have received approval from the Imaging and Radiation Oncology Core (IROC)-Philadelphia RT. The Pre-Treatment Review process requires 3 business days from the receipt of complete data. For each credentialed treating physician and institution, if an unacceptable deviation occurs the next case may require a Pre-Treatment review.

PHYSICIANS/INSTITUTIONS NOT PREVIOUSLY CREDENTIALED FOR HA-WBRT :
A non-credentialed physician may enroll to this trial but will be required to pass successfully 2 pre-treatment reviews on NRG-BN009. Once this requirement has been met the credentialing requirement will have been met in lieu of completing a benchmark case. If the first 2 pre-treatment cases are not acceptable, then the physician/institution will be required to continue with pre-treatment reviews until 2 pre-treatment reviews are successfully passed. Alternatively, if the institution has a previously credentialed physician then that physician will need to review the contours for any future cases until the credentialing requirement has been met. The patient cannot start treatment until they have received approval from the Imaging and Radiation Oncology Core (IROC)-Philadelphia RT.

See Section 13.2 for specifics on submission requirements

At the treating physician's discretion, consolidative SRS boost to selected brain metastases following HA-WBRT is permitted during the follow-up period before radiographic progression of those brain metastases. There are no protocol specifications regarding this consolidative SRS boost.

Treatment Technology

IMRT is required for HA-WBRT on Arm 1. Fixed-gantry IMRT, helical tomotherapy or VMAT can be used. All participating sites must be credentialed for IMRT. Megavoltage beam of 6MV or greater must be used with a minimum source-axis distance of 100cm. The exception is the use of the helical tomotherapy unit that has a source-axis distance of 85cm.

Immobilization and Simulation

Immobilization
Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices.

For HA-WBRT with or without optional simultaneous integrated boost, patients must be immobilized in the supine position using an immobilization device such as an Aquaplast mask

over the head. Patients must be treated in the immobilization device.

Simulation Imaging For HA-WBRT planning with or without optional simultaneous integrated boost, a non-contrast treatment-planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2.5 mm will be required. The axial slice thickness of the treatment-planning CT scan should match the MRI axial slice thickness as much as possible. The treatment-planning CT scan must be acquired with the patient in the same position and immobilization device as for treatment. This should be obtained within 21 days prior to initiating treatment.

Imaging for Structure Definition, Image Registration/Fusion and Follow-up

To yield acceptable image quality, the pre (if performed) and post gadolinium contrast-enhanced three-dimensional SPGR, MP-RAGE, or TFE axial MRI scan should use the smallest possible axial slice thickness not exceeding 1.5 mm. These imaging sequences should be obtained with the patient in the supine position

See Appendix IV for a summary of key imaging requirements.

Downloading MRI Protocol Documents:
If you don't currently have a three-dimensional SPGR, MP-RAGE, or TFE sequence on your scanner, many acceptable examples are available for download from the Alzheimer's Disease Neuroimaging Initiative (ADNI)
http://adni.loni.usc.edu/methods/documents/mri-protocols.

Sites should contact the Neuroradiology or Imaging Co-Chairs for further information or assistance if needed.

Note: The MRI study is mandatory irrespective of randomization to Arms 1 or 2 of this study.

For Arm 1 HA-WBRT planning, the MRI and treatment-planning CT should be fused semi-automatically for hippocampal contouring.

Image fusion between CT and MRI must be performed by a medical physicist and/or treating physician.

Definition of Target Volumes and Margins

For HA-WBRT on Arm 1, the following structures are required and must be named for digital RT data submission as listed in the table below. These structures must be contoured and submitted with the treatment plan. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and

use of underscores must be applied exactly as indicated.

Standard Name	Description	Detailed Specification
CTV_3000	CTV to receive 30 Gy	The whole-brain parenchyma to the foramen magnum.
PTV_3000	PTV to receive 30 Gy	The CTV_3000 excluding the hippocampal avoidance region. No set-up margin is added.

Definition of Critical Structures and Margins

For HA-WBRT on Arm 1, all structures listed in the table below must be contoured and labeled for digital RT data submission as listed. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated. All structures should be contoured on the planning CT, using the fused MRI for guidance as described below. Due to variance in eye position between the CT and MRI, the lenses and optic nerves should be contoured using the CT dataset only.

Standard Name	Description	Descriptive Details
Hippocampi	Bilateral hippocampal contours	Bilateral hippocampal contours will be manually generated on the fused planning MRI/CT image set by the treating physician according to contouring instructions specified on http://www.rtog.org//corelab/contouringatlases/hippocampalsparing.aspx.
Hippocampi_05	Hippocampal avoidance region	Generated by three-dimensionally expanding the hippocampal contours by 5 mm.
Hippo_L	Left hippocampus	Bilateral hippocampal contours will be subdivided into Left and Right hippocampi.
Hippo_R	Right hippocampus	Bilateral hippocampal contours will be subdivided into Left and Right hippocampi.
Lens_L	Left lens	Due to variance in eye position between the CT and MRI, if possible, the left lens should be contoured using the CT dataset only.
Lens_R	Right lens	Due to variance in eye position between the CT and MRI, if possible, the right lens should be contoured using the CT dataset only.
OpticNrv_L	Left optic nerve	Due to variance in eye position between the CT and MRI, if possible, the left optic nerve should be contoured using the CT dataset only.
OpticNrv_R	Right optic nerve	Due to variance in eye position between the CT and MRI, if possible, the right optic nerve should be contoured using the CT dataset only.
OpticChiasm	Optic chiasm	Located above the pituitary fossa, the optic chiasm includes both anterior and posterior limbs. It is best visualized on SPGR/MPR/TFE T1 MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.

Dose Prescription

For HA-WBRT on Arm 1, one treatment of 3.0 Gy will be given daily over approximately 2 weeks for a total of 30.0 Gy (10 fractions). Treatment does not necessarily need to start on a Monday and it is acceptable for treatment to start later in the work week. IMRT plan should be normalized such that 95% of the PTV_3000 volume receives prescription dose of 30 Gy in 10 fractions of 3.0 Gy per fraction. If ≥ 90% of the PTV_3000 volume receives prescription dose of 30 Gy, it will be considered Variation Acceptable .

Compliance Criteria

For HA-WBRT on Arm 1: The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is **required**.

Accuracy of MRI/CT fusion and hippocampal contouring will be assessed subjectively by central physician reviewer. If MRI/CT fusion or hippocampal contouring is not considered acceptable, this will be scored as a Deviation Unacceptable.

NOTE: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.
Target Volume Constraints and Compliance Criteria

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable	Notes
PTV_3000	$D_{2\%}$[Gy]	<= 37.5Gy	>37.5Gy to 40Gy	Dose to hottest 2% of PTV_3000
	$D_{98\%}$[Gy]	>=25Gy	22.5Gy to <25Gy	Dose to 98% of PTV_3000
	$V30_{Gy}$ [%]	>=95%	90% to <95%	Volume receiving prescription dose of 30 Gy

Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Notes
Hippocampi	$D_{100\%}$[Gy]	<=9Gy	>9Gy to 10Gy	Dose to 100% of Hippocampus
	$D_{0.03cc}$[Gy]	<= 16Gy	>16Gy to 17Gy	Dose to hottest

				0.03 cc volume of Hippocampus
OpticNrv_L	$D_{0.03cc}$[Gy]	<=30Gy	>30Gy to 37.5Gy	Dose to hottest 0.03 cc volume of OpticNerve_L
OpticNrv_R	$D_{0.03cc}$[Gy]	<=30Gy	>30Gy to 37.5Gy	Dose to hottest 0.03 cc volume of OpticNerve_R
OpticChiasm	$D_{0.03cc}$[Gy]	<=30Gy	>30Gy to 37.5Gy	Dose to hottest 0.03 cc volume of OpticChiasm

Delivery Compliance Criteria

	Per Protocol	**Variation Acceptable**	**Notes**
Interruptions	0 break days	1-3 break days	Unscheduled break days

Treatment Planning Procedures and Priorities

For HA-WBRT on Arm 1: Intensity-modulated radiotherapy will be used for patients enrolled in the WBRT with hippocampal avoidance arm. In optimizing planning, the following treatment-planning priorities should be followed:

1. OpticChiasm
2. OpticNrv_L or OpticNrv_R
3. Hippocampus
4. PTV_3000
5. Lens_L or Lens_R

In the event that an OAR with higher priority than PTV_3000 cannot be constrained within Unacceptable Deviation limits, then D98% and/or V30Gy for PTV_3000 should be lowered to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits.

Dose Calculations

For HA-WBRT with or without optional simultaneous integrated boost on Arm 1:
Primary dataset for dose calculation should be non-contrast treatment-planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2.5 mm. Dose matrix grid size must be ≤ 3 mm in sagittal and coronal directions.

Patient-Specific QA

For HA-WBRT on Arm 1: Patient-specific QA is strongly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 4% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan. These QA data will not be collected but should be held by the institution and available for review if requested.

Daily Treatment Localization/IGRT

Verification orthogonal films or images that localize the isocenter placement shall be obtained. The length of the treatment field shall be indicated on these films. These films will not be collected but should be held by the institution and available for review if requested.

5.2.2 Arm 2: SRS/fractionated SRS (fSRS)

Treatment Technology

This protocol requires photon treatment. GammaKnife or linear accelerator-based treatments with nominal x-ray energy of 6MV or greater (including isocentric conical collimators, MLC, or linear accelerators mounted on robotic arms) are allowed. The treatment machines must be commissioned for small field sizes. Credentialing for SRS head phantom irradiation from IROC Houston is mandatory. 3D-CRT (including static and dynamic MLC arcs), IMRT techniques (including Tomotherapy and VMAT) are allowed.

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices. Both invasive frame-based immobilization and non-invasive thermoplastic mask-based immobilization are allowed.

Simulation Imaging

Contiguous CT slices of 1.25 mm slice thickness or less should be obtained. CT scan should cover from top of head to bottom of skull. Post gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan (as defined in Section 3.2) is required for target delineation.

> **Downloading MRI Protocol Documents:**
> If you don't currently have a three-dimensional SPGR, MP-RAGE, or TFE sequence on your scanner, many acceptable examples are available for download from the Alzheimer's Disease Neuroimaging Initiative (ADNI) *http://adni.loni.usc.edu/methods/documents/mri-protocols.*

Sites should contact the Neuroradiology or Imaging Co-Chairs for further information or assistance if needed.

See Appendix IV for a summary of key imaging requirements.

Image fusion between CT and MRI must be performed by a medical physicist and/or treating physician.

For radiosurgical modalities (e.g., GammaKnife) where MRI can be used for treatment planning, CT is not required.

Definition of Target Volumes and Margins

Target names:

GTV(1-9)_	Frontal_	L_ or R_	XXXX (cGy)
CTV(1-9)_	Parietal_	L_ or_R_	XXXX (cGy)
PTV(1-9)_	Cerebellum_	L_ or R_	XXXX (cGy)
	Temporal_	L_ or R_	XXXX (cGy)
	Occipital_	L_ or R_	XXXX (cGy)
	Brainstem_	(No Lateral)	XXXX (cGy)

Detailed Specifications

GTV: The GTV is defined as the enhancing metastasis on a gadolinium-enhanced 3D SPGR MRI scan.

CTV: CTV is defined as identical to GTV.

PTV: The PTV is defined as identical to CTV or as the CTV plus an optional volumetric 1.0mm margin.

If GTV=CTV=PTV (i.e., no PTV margin utilized), then only the PTV target needs to be generated for SRS planning and submitted for central review.

For cases using single isocenter multitarget, the 1.0mm PTV margin is recommended.

Definition of Critical Structures

Note: All structures must be named for digital RT data submission as listed in the table below. Structures marked as "Required when applicable" must be contoured and submitted when applicable (e.g., metastasis close to structure)

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Standard Name	Description	Importance **(Required/Required when applicable/Optional)**
BrainStem	Brainstem	Required when applicable
OpticChiasm	Chiasm	Required when applicable
OpticNrv_L	Left optical nerve	Required when applicable
OpticNrv_R	Right optical nerve	Required when applicable

Dose/Volume Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

Single fraction SRS:

Arm 2: SRS.

PTVs with maximum dimension <1.0 cm receive 24 Gy
PTVs with maximum dimension ≥1.0 cm to <2.0 cm receive 22 Gy
PTVs with maximum dimension ≥2.0 cm to <3.0 cm receive 18 Gy

For brain stem lesions, peripheral doses of 18-20 Gy, 16-18 Gy, and 14-16 Gy should be used for tumor volumes of less than 1 cm^3, 1-4 cm^3, and 4-10 cm^3, respectively.

The dose is prescribed to the isodose line encompassing at least 99% of the PTV.

Fractionated SRS (fSRS):

Note: At the physician discretion, fractionated SRS may be used. In patients where single-fraction SRS planning leads to a per-lesion brain (normal brain plus target volume) V12 >10cc, fractionated SRS is encouraged to lower risk of radiation necrosis. Please contact study PIs for questions.

Arm 2: fSRS.

PTVs with maximum dimension <3.0 cm receive 27 Gy/ 3 fractions	

For brain stem lesions, peripheral doses of 21 Gy should be used for tumor volumes of ≤10 cm^3, respectively.

The dose is prescribed to the isodose line encompassing at least 99% of the PTV.

Compliance Criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment-planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met

Target Volume Constraints and Compliance Criteria for SRS and fSRS

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Notes
PTV	D99%[%]	100%	95% to 105%	Dose (%) to 99% of PTV
	D0.03cc[%]	<=120%	>120% to <=125%	Maximal dose (%) to 0.03cc
	Conformity Index	<=1.5*	> 1.5 to <=2.0*	Ratio of prescription isodose volume over the PTV volume

*Does not apply to lesions having a volume of less or equal than 0.1 cm^3.

Normal Structure Constraints and Compliance Criteria

Single fraction SRS:

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
BrainStem	D0.03cc[Gy]	<=12Gy	>12Gy to < 14Gy
	D1%[Gy]	<=10Gy	>10Gy to < 12Gy

OpticChiasm, OpticNrv	D0.03cc[Gy]	<=8Gy	>8Gy to < 10Gy

Fractionated SRS:

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
BrainStem	D0.03cc[Gy]	<=23.1Gy	>23.1Gy to < 24.1 Gy
	D0.5cc[Gy]	<=18Gy	>18Gy to < 20Gy
OpticChiasm, OpticNrv	D0.03cc[Gy]	<=17.4Gy	>17.4Gy to < 19.5 Gy
OpticChiasm, OpticNrv	D0.2cc[Gy]	<=13.8Gy	>13.8Gy to < 15.3Gy

Delivery Compliance Criteria

	Per Protocol	Unacceptable Deviation
Start date	<= 21days days after randomization	>21 days after randomization

Treatment Planning Priorities and Instructions

For SRS/fSRS on Arm 2: In optimizing planning, the following treatment-planning priorities should be followed:

1. BrainStem*
2. OpticChiasm, OpticNrv_L, OpticNrv _R
3. PTV1, PTV2, …

*For brainstem metastases, PTV exceeds brainstem in treatment planning priorities.

In the event that an OAR with higher priority than a PTV cannot be constrained within Unacceptable Deviation limits, then D99% and/or D0.03cc and/or Conformity Index for that PTV should be lowered to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits.

- Required algorithms
Acceptable choices of algorithm are listed at http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf. Besides the algorithms listed, the pencil beam algorithm is also allowed in this protocol. Any algorithm used for this study must be credentialed by IROC Houston.

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided.

Dm, computed inherently by these algorithms, should be reported. These principles hold for Pencil Beam type algorithms and for homogeneous dose calculations when allowed for a clinical trial (e.g., conical collimators in stereotactic radiosurgery).

- Primary dataset for dose calculation
Planning CT image is the primary dataset for dose calculation. In case MR image is used for dose calculation, a method of correcting image distortion and tissue density has to be applied to get accurate body contour and heterogeneity corrections. Periodic phantom QA is a must to verify its linearity.

-Dose matrix resolution
Dose grid size should be ≤ 1.25 mm in all directions.

-Potential radiosurgical techniques include 3D conformal beams, static MLC arcs, dynamic conformal MLC arcs, cone-based arcs, IMRT, VMAT, GammaKnife, CyberKnife, or combination of different techniques.

Using single isocenter to treat multiple targets at same time is allowed with VMAT technique (or other published equivalent techniques). By doing so, dosimetric compliance criteria should be evaluated for each target individually. An end-to-end test for this type of technique is strongly recommended.

- Take all measures to ensure a plan is deliverable including embodying collision clearance checks prior to treatment.

Patient-Specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines.

For photon IMRT plans, patient specific QA is mandatory. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 2 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

Daily Treatment Localization/IGRT

For SRS treatment, IGRT is mandatory except for invasive frame-based setup on GammaKnife treatment. The use of IGRT permits elimination of the margin of PTV. Image guidance methods include 2D x-ray, 3D x-ray, electromagnetic localization, optical surface imaging, and others. Image registration techniques can include bone as surrogate, fiducial markers, and/or soft tissue. Localization checks are per institutional guidelines but recommended after each patient shift.

Daily treatment check sheet
Prior to delivery of radiation, develop a verification checklist. The checklist should include

collision clearance check for each radiation delivery field, final patient position verification signed by physician, etc. Therapist and physicist sign off of each step.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

Herbal and Nutritional Supplement

The concomitant use of herbal therapies is generally not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However the use of general nutritional foundation supplements will be allowed including: calcium with vitamin D and/or minerals, Omega3s (fish oil), Vitamin B6, Vitamin B12, basic multivitamins, L-glutamine, or probiotics oral supplements will be permitted either at or below the recommended dosing by a healthcare provider. Herbal-based multivitamins are not allowed.

Concomitant Medication Precautions

The clearance of memantine is reduced with alkaline urine conditions at pH 8 or higher. Urine pH can be made more alkaline with chronic use of carbonic anhydrase inhibitors (e.g. acetazolamide, brinzolamide, methazolamide, dorzolamide, topiramate) and sodium bicarbonate and hence, memantine should be used with caution with these medications. Concurrent use of memantine with other NMDA antagonists (e.g. amantadine, ketamine, or dextromethorphan) is an exclusion criterion, and other medications should be considered.

5.3.2 Participation in Other Trials

Patients are not to participate in other radiotherapeutic trials. Patients may participate in trials that do not test radiotherapy questions, including trials of novel systemic therapy agents. However, the ineligibility criterion 3.2.5 should be carefully considered.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 Memantine

Approximately 50% of memantine is metabolized by the liver; the remaining 50% is excreted unchanged by the renal system. Separate tables are provided for twice daily or extended release dosing of memantine.

6.1.1 Twice Daily Dosing

A dosage reduction to 5 mg orally twice daily is recommended in patients with severe renal impairment [creatinine clearance (CrCl), 5 to 29 milliliters/minute (mL/min)]. Therefore the eligibility criterion for creatinine clearance is ≥ 30 mL/min and no dosage adjustment is needed in patients with mild (CrCl greater than 50 to 80 mL/min) or moderate (CrCl 30 to 49 mL/min) renal impairment.

Creatinine should be evaluated at each follow-up evaluation. Memantine will be dose modified based on criteria outlined in the dose modification table below.

% Calculated Dose

***Creatinine Clearance (CrCl) (ml/min)**		
≥30	**5-29**	**<5**
10 mg by mouth twice daily	5 mg by mouth twice daily Recheck value weekly; If CrCl not > 29 (mL/min) by 3 weeks, continue at reduced dose throughout protocol treatment.	HOLD STUDY DRUG Recheck value weekly; If CrCl not > 5 (mL/min) by 3 weeks, discontinue memantine

* For males: CrCl = [140-age (years)] · *Weight (kg)/[72 · serum creatinine (mg/dL)]
For females: CrCl = 0.85 · [140-age (years)] · *Weight (kg)/[72 · serum creatinine (mg/dL)]
*Actual weight should be used unless patient is greater than 30% above IBW, then used Adjusted BW (= IBW + 0.4*actual BW) in the Cockcroft Gault equation.

6.1.2 Extended Release Dosing

A dosage reduction to 14 milligrams (mg) orally daily is recommended in patients with severe renal impairment (creatinine clearance (CrCl), 5 to 29 milliliters/minute (mL/min)). Therefore the eligibility criteria is for creatinine clearance ≥ 30 ml/min and no dosage adjustment is needed in patients with mild (CrCl greater than 50 to 80 mL/min) or moderate (CrCl 30 to 49 mL/min) renal impairment.

Creatinine should be evaluated at each follow-up evaluation. Memantine will be dose modified based on criteria outlined in the dose modification table.

% Calculated Dose

***Creatinine Clearance (CrCl) (ml/min)**		
≥30	**5-29**	**<5**
28 mg by mouth daily	14 mg by mouth daily Recheck value weekly; If CrCl not > 29 (mL/min) by 3 weeks, continue at reduced dose throughout protocol treatment	HOLD STUDY DRUG Recheck value weekly; If CrCl not > 5 (mL/min) by 3 weeks, discontinue memantine

* For males: CrCl = [140-age (years)] · *Weight (kg)/[72 · serum creatinine (mg/dL)]

For females: CrCl = 0.85 · [140-age (years)] · *Weight (kg)/[72 · serum creatinine (mg/dL)]
*Actual weight should be used unless patient is greater than 30% above IBW, then used Adjusted BW (= IBW + 0.4*actual BW) in the Cockcroft Gault equation.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Commercial Agents

The commercial agent in NRG-BN009 is memantine.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Adverse Events for Commercial Study Agent: Memantine

Refer to the package insert for detailed pharmacologic and safety information

7.4 Expedited Reporting of Adverse Events (06-APR-2023)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://ctepcore.nci.nih.gov/ctepaers/security/login

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited

adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS-24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Deidentified supporting source documentation should be uploaded to the Source Document Portal via the CTEP-AERS integration.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.4.2 Expedited Reporting Requirements for Adverse Events Any Phase Study Utilizing Standard of Care Treatment[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected

Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day		24-h/5 day	24-h/5 day

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of **possible, probable, or definite** require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- Unexpected Grade 4 and all Grade 5 AEs

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements

None

7.4.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.4.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

7.5 Routine Reporting Requirements for Adverse Events

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

7.6 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (06-APR-2023)

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam.Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability..

RCR utilizes five person registration types.

- Investigator (IVR)— MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP)— clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts, and by July 1, 2023 for all users) is required to participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI must be rostered at the enrolling site with a participating organization (i.e., Alliance). Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures (06-APR-2023)

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support System Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to

the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);

- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only);
- Compliance with all applicable protocol-specific requirements (PSRs)

Protocol-Specific Requirements for Protocol NRG-BN009 Site Registration

- IRB/REB approved consent (International and Canadian sites only: English and native language versions) English version must be submitted to NRG Regulatory (Regulatory-PHL@nrgoncology.org) for review prior to IRB/REB/IEC submission. **Note**: International and Canadian Institutions must provide certification/verification of IRB/REB/IEC consent translation to NRG Oncology (described below).

  Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB/IEC approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational letterhead/stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider for SRS and IMRT. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section of the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Site must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.

- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

To complete protocol-specific credentialing the RTI provider or enrolling site

should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory and Roster Maintenance applications to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification. . IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in the Regulatory application, the enrolling site may access Oncology Patient Enrollment Network (OPEN) to complete enrollments. If the study is using the IROC integration suite, the enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist..

- Neurocognitive Function Testing Certification
  Institutions must meet certification requirements for administering neurocognitive assessments. Upon review and successful completion of the Neurocognitive Certification, Dr. Jeffrey Wefel will notify both the certified examiner and NRG Headquarters that the examiner has successfully completed this requirement. See protocol-specific material on CTSU website for certification requirements

Additional Requirements for sites in Canada

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines [per section 6.2.5 of ICH E6(R2)]. This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result essential documents must be retained for 15 years following the completion of the trial at the participating site (15 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by the sponsor, NRG Oncology, that documents no longer need to be retained [per C.05.012 (4) of the FDR]. In addition, upon request by the auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access [per section 4.9.7 of ICH]. Prior to clinical trial commencement, sites in Canada must also complete and submit to NRG Regulatory (Regulatory-PHL@nrgoncology.org):

- Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
- Protocol Signature Page
- Delegation of Tasks (DTL) Log
- List of Laboratories
- SIV/Training Confirmation of Completion Form – Research Associate (please refer to the activation memo for details)

- SIV/Training Confirmation of Completion Form – Qualified Investigator (please refer to the activation memo for details)
- IRB/REB approved consent (English and native language versions).

The following items are collected By NRG Oncology Regulatory on a yearly or biyearly basis:

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL log

Record Retention: The sponsor, NRG Oncology, shall maintain records identified in *Health Canada guidelines Part C, Division 5, section C.05.012* for a period of at least 15 years.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number *NRG-BN009*;
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log on to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the site's 5-character CTEP Institution Code and click on Go:
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

8.2 RT-Specific Pre-Registration Requirements (06-APR-2023)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. IROC will automatically send the approval to the Regulatory Support System (RSS) to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification The credentialing notification document (email) must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality	
	photons	Key Information

Credentialing Status Inquiry Form	**X**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Facility Questionnaire	**X**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Phantom Irradiation	**X**	A SRS phantom study and IMRT HN phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantoms are found on the IROC Houston web site (**http://irochouston.mdanderson.org**).
Pre-treatment	**X**	A non-credentialed physician may enroll to this trial but will be required to pass successfully 2 pre-treatment reviews on NRG-BN009. Once this requirement has been met the credentialing requirement will have been met in lieu of completing a benchmark case and the site can request a credentialing letter by completing a CSI form. If the first 2 pre-treatment cases are not acceptable, a credentialed physician from your site will need to review the contours for any future cases. See 5.2.2 for more details
Credentialing Notification Issued to:		
Institution		Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

8.2.1 Digital Radiation Therapy Data Submission Using Transfer of Images and Data

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
- TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have

access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.3 Patient Enrollment (06-APR-2023)

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.3.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.4 Medidata Patient Cloud ePRO Registration (06-APR-2023)

This study includes the use of Medidata's Patient Cloud ePRO (electronic patient-reported outcomes) application. The Patient Cloud mobile ePRO application allows patients to report clinical trial information (patient reported outcomes (PRO)) directly from their mobile devices into the Medidata Clinical Cloud. In this document *ePRO application* refers to the application accessed by the site via iMedidata (for patient registration) and Rave (to view completed ePRO forms), and *Patient Cloud mobile ePRO app* refers to the app accessed by the patient on a mobile device. After the patient is registered to the trial via OPEN, and if the patient is willing to participate in electronic data collection, the site staff will then complete a registration for the patient to the ePRO application through iMedidata. Site staff must complete the required eLearning (assigned in iMedidata) for the ePRO application before registering a patient. Information about the training is in Appendix I. The registration to the ePRO application will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the appropriate ePRO mobile app onto his/her own device (iOS (Apple), Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial.

There are multiple versions of the ePRO mobile app available. Ensure that the correct version of the Patient Cloud mobile ePRO app is downloaded by the patient. Note only 1 version of the app is active per protocol and this protocol is using:
The mobile app named simply "Patient Cloud" that has this icon in the app stores:

For sites providing a shared institutional device for use by multiple patients on site: The site staff should assist the patient with registration to the ePRO application and access to the Patient Cloud mobile ePRO app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

8.4.1 CRA Patient Registration Instructions for Patient Cloud

Site staff must complete the required ePRO online training (assigned in iMedidata) for studies using the ePRO application before registering a patient. Reference materials for the Patient Cloud (current) app can be found at the link below (iMedidata login is required); the landing page contains general information as well as links to additional resources on the left side of the screen:
Patient Cloud (current) Medidata Learning Tool

The subject registration process starts in iMedidata. To register a patient log into iMedidata and perform the following steps:

i. Select the Patient Cloud Registration link for your study
ii. From the patient management app, select your STUDY and SITE from the drop downs and click Launch.
iii. Register your first patient. Create a subject ID and select a Country / Language from the drop down (required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.
iv. The subject will be added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

Reminder- site staff must have already completed the Medidata Patient Cloud training in order to register study participants. Please visit the CTSU website for reference information.

9. DRUG INFORMATION

9.1 Commercial Agent: Memantine

Sites are permitted to prescribe and dispense either memantine immediate release or extended release tablets. Sites must refer to the package insert for detailed pharmacologic and safety information.

9.1.1 Adverse Events

Please refer to the package insert.

9.1.2 Availability/Supply

Please see Section 5.1 for administration instructions. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.)

10. PATHOLOGY/BIOSPECIMEN

10.1 Biospecimen Submission Tables (06-APR-2023)

10.1.1 Optional Specimen Submissions

(Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.)

A detailed description of biospecimen collection and submission procedures can be found in the Biospecimen Collection and Submission Manual (found on the CTSU protocol page under the Protocol Related Documents tab).
This study will include collection of biospecimens for future analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

Optional Study Description #1: Serum Analysis for Exosomal MicroRNA and Cytokine Profiling

Specimen Type	Collection Time Points	Collection Information and Requirements/Instructions for Site	Shipping
Serum- Red top tube	Pre-treatment Within 21 days before SRS/fSRS or HA-WBRT Post-treatment Within 2 months of start of SRS/fSRS or HA-WBRT	Storage: -80°C and ship frozen Forms: ST form Kits: request from NRGBB-SF. Shipping: Prepaid label provided	Batch Ship frozen on dry ice by overnight courier to NRGBB-SF.

Optional Study Description #2: Biobanking for Future Research

1) Kits are available for frozen biospecimens from the NRGBB-SF. Send an email to NRGBB@ucsf.edu requesting a kit. Allow 5-10 business days for kits to arrive by Fed EX Ground delivery.
2) Shipping days for frozen specimens: Monday-Wednesday (US sites); Monday-Tuesday (Canadian sites).
3) Shipping costs- One prepaid return label per case for batch shipping of frozen specimens will be provided in the US kits from the NRGBB-SF.
4) Brief processing instructions are provided with kits, and complete versions are available in NRG-BN009 Pathology and Correlative Science Instructions document posted on the CTSU website.

For questions, contact:
NRG Oncology Biospecimen Bank – San Francisco
UCSF Department of Radiation Oncology
2340 Sutter Street- Room S341
San Francisco, CA 94115
415-476-7864/Fax 415-476-5271
Email: NRGBB@ucsf.edu

Specimen Type	Collection Time Points	Collection Information and Requirements/Instructions for Site	Shipping
Serum- Red top tube	Pre-treatment Within 21 days before SRS/fSRS or HA-WBRT Post-treatment Within 2 months of start of SRS/fSRS or HA-WBRT	***May be residual from Optional Study Description #2 above*** Storage: -80°C and ship frozen Forms: ST form Kits: request from NRGBB-SF. Shipping: Prepaid label provided	Batch Ship frozen on dry ice by overnight courier to NRGBB-SF.

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Patient-Reported Quality of Life (QOL) and Neurocognitive Function (NCF)
(06-APR-2023)

11.1.1 QOL Background and Assessments

Symptom burden will be assessed using the MDASI-BT-modified (Armstrong 2006). The MDASI-BT has demonstrated reliability and validity in the primary brain tumor patient population, including predictive validity for tumor recurrence (Armstrong 2006, Armstrong 2011). The MDASI-BT was developed and validated for use in the brain tumor patient population and typically requires less than 4 minutes to complete. It consists of 23 symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being "not present" and 10 being "as bad as you can imagine." Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument are those commonly associated with cancer therapies and those associated with neurologic and cognitive symptoms associated with the tumor itself. The MDASI-BT also includes ratings of how symptoms have interfered with different aspects of the patient's life in the last 24 hours. These interference items include: general activity,

mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0-10 scales.

Health-related quality of life will be assessed using the EQ-5D-5L and PROMIS Cognitive Function Short Form 4a v2.0. The EQ-5D-5L is a standardized self-report measure of health status developed by the EuroQOL Group in order to provide a simple, descriptive profile and a single index value for clinical and economic appraisal (Oemar 2013). The initial EQ-5D was adapted to include a 5-level measure of severity to improve reliability and sensitivity and reduce ceiling effects. It consists of 2 pages, the EQ-5D-5L descriptive (mobility, self care, usual activities, pain/discomfort, anxiety/depression) using 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems) and the EQ Visual Analogue scale (EQ VAS). The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine', with respondents marking an X on the scale to indicate health today and then writing the number marked on the scale in a box below. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. The 4-item PROMIS form was found to be highly correlated with the 8-item measure and has demonstrated excellent internal consistency and reliability (Safer 2015, Cella 2015), and has criterion validity related evidence for measuring cognitive concerns (Valentine 2019).

11.1.2 NCF Background and Assessments

NCF will be assessed using the Hopkins Verbal Learning Test – Revised (Benedict 1998), Trail Making Test (Tombaugh 2004), and the Controlled Oral Word Association test (Ruff 1996). These tests were selected because they are widely used and standardized psychometric instruments that have been shown to be sensitive to the impact of cancer and the neurotoxic effects of cancer treatment in other clinical trials (Wefel 2011, Gilbert 2014, Meyers 2004). The tests have published normative data that take into account age and, where appropriate, education and gender. The tests must be administered by a healthcare professional (eg, psychologist, physician, research associate, nurse) who is pre-certified by Dr. Wefel (see Section 8.1).

11.1.3 Administration of NRG-BN009 Patient-Completed Questionnaires and NCF Assessments

Patient Population

All patients enrolled in NRG-BN009 who speak English or live in Canada and speak French will be required to participate in the QOL/NCF study. Speakers of other languages are not permitted to participate in the QOL/NCF study.

Time Points for Administration

See Section 4.

Administration Instructions

After the baseline, QOL questionnaires may be completed using the Patient Cloud mobile ePRO application (discussed in Section 8) or on paper at the visit. If the patient

chooses to complete on paper, questionnaires are to be administered at follow-up visits, so that when a follow-up visit is delayed, completion of QOL may also be delayed. QOL should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaires are completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by mail or phone. The completed form will then be data entered into Medidata Rave.

The QOL Coversheets must be completed in Medidata Rave for each scheduled patient assessment regardless of whether the assessment was completed or not. The Coversheets notify the NRG SDMC that an assessment either has or has not been completed and collects other important information. If the assessment was completed, the Coversheet collects the date of completion and method of completion. If the assessment was not completed, the Coversheet collects the reason it was not completed. The questionnaires can be completed by phone or mail if they are not completed at an office visit.

The Neurocognitive Function Verification form must also be completed in Medidata Rave whether or not the Neurocognitive Function assessment was completed.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

The Principal/Co-Principal Investigators/Radiation Oncology Co-Chairs (Vinai Gondi, MD; Michael Chan, MD) and/or NRG Oncology Headquarters–approved designees will perform an RT Quality Assurance Review after IROC Philadelphia-RT has received complete data in TRIAD. Pre-treatment reviews for HA-WBRT will be reviewed within 3 business days of submission of complete data. Reviews for all other cases (SRS and post-hoc HA-WBRT) will be ongoing and performed remotely. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as IROC-Philadelphia RT has received complete data in TRIAD for all cases enrolled, whichever occurs first. The scoring mechanism is: **Per Protocol, Variation Acceptable, and Unacceptable Deviation**.

12.2 Drug Quality Assurance Reviews

The Neuro-Oncology Co-Chair (Rimas Lukas, MD) or NRG Oncology Headquarters–approved designee will perform a Quality Assurance Review to evaluate memantine protocol compliance. The review process is contingent on timely submission of treatment data. The scoring mechanism is: **1) Per Protocol, 2) Acceptable Variation, 3) Unacceptable Deviation, and 4) Not Evaluable.**

Dr. Lukas/designee will perform a Quality Assurance Review after NRG Data Management Center has received complete data for cases enrolled. The reviews will be ongoing and performed remotely. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Data Management Center has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

13.1 Data Management/Collection (06-APR-2023)

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users); and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are

completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

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13.2 Summary of Data Submission (06-APR-2023)

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting.

Summary of All Data Submission: Refer to the CTSU website

See Section 8 for TRIAD account access and installation instructions. See data submission table for TRIAD below.

ARM 1 HA-WBRT IMRT submission requirements

DICOM Items	DICOM CT Image	**Due Within 1 week of start of RT.** **For Pre-treatment reviews submit for review prior to RT; 3 Business days required from submission of complete data.** Triad Time Point: *RT Digital Plan*
	DICOM Structure	
	DICOM Dose	
	DICOM Plan	

All required structures must be labeled per the tables in Sections 5.2.1 5.2.2	
Imaging needed for RT review:	
Entire MRI used with Planning CT must be submitted with RT data. Pre-treatment reviews cannot be completed without submission of the MRI. MRI sequences to be submitted are: MP-RAGE, TSE, axial T2 or axial T2 FLAIR (PREFERRED) sequences, and gadolinium contrast-enhanced three-dimensional SPGR. Please submit ADC, DWI, pre-contrast axial T1 (3D strongly encouraged) imaging if available.	Triad Time Point: *Baseline*
Upon submission of the digital data via TRIAD, complete an online **Digital Data Submission Information Form (DDSI)**: https://www.irocqa.org/Resources/TRIAD	
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.	

ARM 2 SRS submission requirements

DICOM Items	DICOM CT/MR Image	**Due Within 1 week of start of RT.** TRIAD Time point: *RT Digital Plan Modified*
	DICOM Structure	
	DICOM Dose	
	DICOM Plan	
All required structures must be labeled per the tables in Sections 5.2.4 5.2.5		
Submit a redacted PDF of the treatment plan via TRIAD		
Imaging needed for RT review:		
Post gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan Post gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo		Triad Time Point: *Other*

(MP-RAGE), or turbo field echo (TFE) MRI scan . For radiosurgical modalities (e.g., GammaKnife) where MRI can be used for treatment planning, CT is not required.	
Upon submission of the digital data via TRIAD, complete an online **Digital Data Submission Information Form (DDSI)**: https://www.irocqa.org/Resources/TRIAD	

NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.

DIAGNOSTIC MRI IMAGING REQUIRED FOR SUBMISSION TO TRIAD

MRI Brain in its entirety: See bullets below for required MRI sequences. Please still submit ENTIRE MRI Brain exam.	TRIAD Time Points*:
• MRI with Axial T2 FLAIR (preferred) or axial T2 TSE/FSE images required. • Pre and Post Gadolinium contrast-enhanced three-dimensional (3D) images required.	Baseline Follow-up

Please reference appendix IV for specific MRI imaging parameter guidelines for 3D sequences. Please also submit ADC and DWI imaging if available.

Please ensure selection of the correct imaging time point in TRIAD.

To ensure anonymity of our trial patients, TRIAD is uniquely configured to remove and/or re-identify Protected Health Information (PHI) from image metadata during the image submission process.

Do not apply any further anonymization to any exam prior to uploading into the TRIAD application.

Essential data which must be preserved includes the study date, scanner station name, scanner serial number and scan acquisition parameters. Any further anonymization prior to submission via TRIAD may exclude an exam from final analysis due to the omission of these important technical elements.

While TRIAD can de-identify all PHI within DICOM image metadata, some files stored in imaging PACS systems may include data that TRIAD cannot anonymize automatically (including patient questionnaires, dose reports, and other electronic records). For these file types:

- Expand all series within the TRIAD Preview Window
- Deselect files which may contain PHI before moving them to the submission queue (these include files such as protocol pages, patient reports, questionnaires, and study orders)
- Prior to submitting, you may also utilize the Clean Pixel Tool within TRIAD to redact any PHI that has been “burned into” images

Consult with your PACS administrator or contact the IROC Philadelphia Core Laboratory for further information.

*Only submit diagnostic imaging specified in the protocol (Required assessments can be located in section 4).

13.3 Data Quality Portal (06-APR-2023)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms. DQP Form Status, and DQP Reports modules.

13.4 Global Reporting/Monitoring

Required submission of patient demographic data for this study will be submitted automatically via OPEN.

Note: Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design (06-APR-2023)

NRG-BN009 is a randomized phase III trial to determine if hippocampal-avoidant whole brain radiotherapy (HA-WBRT) with memantine in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year prolongs time to

neurologic death as compared to stereotactic radiosurgery (SRS).

14.1.1 Randomization

Patients who meet the eligibility criteria will be randomized using permuted block randomization in a 1:1 randomization ratio to SRS arm (control arm) or HA-WBRT arm (experimental arm). Randomization will be stratified by: BMV (>13 vs. 4-13), DS-GPA at time of last SRS (≤2 vs. >2) and receiving immunotherapy at time of enrollment (yes vs. no).

14.1.2 Total Accrual

This trial will enroll a total of 350 patients.

14.2 Study Endpoints

14.2.1 Primary Endpoint

The primary endpoint is time to neurologic death defined as time from randomization until progressive neurologic decline at time of death, irrespective of status of extracranial disease, or death from inter-current disease in patients with severe neurologic dysfunction.

14.2.2 Secondary Endpoints

- Overall survival, defined as time from randomization to death from any cause
- Intracranial progression-free survival, defined as time from randomization to intracranial progression or death from any cause
- Brain metastasis velocity at subsequent relapse
- Neurocognitive function outcomes
- Cognitive abilities, symptom burden and health status, as measured by MDASI-BT, PROMIS cognitive function, and EQ-5D-5L
- Adverse events associated with the interventions
- Number of salvage procedures and estimated cost of brain-related therapies

14.3 Primary Objectives Study Design (06-APR-2023)

14.3.1 Primary Hypothesis and Endpoints

The primary endpoint for this randomized phase III study is time to neurologic death. Detailed definition of this endpoint is given in Section 4. The null hypothesis is that HA-WBRT in patients with brain metastasis velocity ≥4 new brain metastases per year since last SRS will be equivalent in terms of time to neurologic death as compared to salvage SRS alone. The alternative hypothesis is that HA-WBRT in patients with brain metastasis velocity ≥4 new brain metastases per year will decrease the 12-month neurologic death rate to 24%, as compared to 34% in the SRS arm. This improvement corresponds to a 38% relative hazard reduction (HR of 0.621) in favor of the HA-WBRT arm, assuming exponential distribution.

14.3.2 How Primary Endpoints Will Be Analyzed

The definitive primary endpoint analysis for this phase III trial will be conducted after 127 neurologic death events (among both treatment arms) have been recorded. The primary analysis will be done on an intent-to-treat basis, such that all eligible and randomized cases on the study will be included in the arm to which they are randomized regardless of what treatment the patients actually received. The primary comparison of treatment effect on neurologic deaths will be based a one-sided 0.05-level (score) test for cause-specific hazard ratio (CHR) in a Cox proportional hazards

model. If the associated one-sided p-value is 0.05 or less, then the trial will conclude that HA-WBRT prolongs time to neurologic death over SRS.

Additional analyses will involve estimating the median time to neurologic death using the cumulative incidence function estimator in the presence of precluding events such as non-neurologic deaths in the two arms, separately (Korn 1992). The Gray's test will be used to evaluate the difference in the distribution of neurologic deaths (Gray 1988). These results will be interpreted in light of the competing non-neurologic deaths, which may be frequent.

14.3.3 Sample Size and Power Calculations

Due to the competing risk of non-neurologic death, the method described by Pintilie is used for the sample size estimation. It is assumed that the 12-month neurologic death rate is 34.0% in the SRS group based on results from Farris et al (2017), and that the 12-month rate for non-neurologic death is the same for both arms, at 38.9%. It is projected that HA-WBRT would reduce the 12-month neurologic death rate by 10%, which corresponds to a hazard ratio (HR) of 0.621 for HA-WBRT with respect to SRS. Assuming uniform accrual of 333 patient over 33 months (at 10 pts/month accrual rate) with an additional 12 months follow-up after accrual completion, this design will give 85% statistical power to detect the targeted HR of 0.62 (experimental vs. control) using a 1-sided 0.05-level (score) test for cause-specific hazard ratio (CHR) in a Cox proportional hazards model, based on the assumed incidence rates for neurologic deaths and non-neurologic deaths (competing risk) above (Pintilie). The primary analysis will be event-driven and will be conducted when a total of 127 events (neurologic deaths) have been observed. The trial will over-accrue by 5% (i.e. for a total of 350 patients) to account for ineligibility, early consent withdrawal, lack of follow-up, etc.

14.4 Study Monitoring of Primary Objectives (06-APR-2023)

The trial is monitored on a continuous basis during conduct, including a monthly tally of accrual, real-time oversight of serious adverse events as required, and regular meeting of the study team to track progress and identify problems.

Interim Reports to Monitor Study Progress

Reports will be prepared twice per year until the initial treatment results have been presented/published. The interim reports will contain at a minimum the following information:

- Total patients accrued, patient accrual rate and projected accrual completion date (while the study is still accruing), and information on trial eligibility of patients enrolled
- Frequency distributions of important patient and disease characteristics by treatment arm
- Frequencies and severity of adverse events by treatment arm

DMC Reviews

The NRG Oncology Data Monitoring Committee (DMC) will review the trial twice a year, with respect to patient accrual, morbidity, and timeliness of data reporting. The

DMC also will review the study for the protocol-specified primary endpoint interim analysis, as well as on an "as needed" basis if the need arises.

14.4.1 Interim Futility Monitoring

One interim futility analysis for the primary endpoint of neurologic death will be performed when about 50% of the expected number of events (i.e. 64 neurologic deaths) have occurred. The futility analysis will be based on testing treatment effect on neurologic deaths using a 1-sided 0.4 level (score) test for cause-specific hazard ratio (CHR) in a Cox proportional hazards model. The analysis will be done on an intent-to-treat basis.

To evaluate the operating characteristics of the proposed futility monitoring rule in the context of this trial, we conducted 5,000 Monte-Carlo simulations for a number of significance levels for the futility test (namely, 0.30, 0.40, 0.50). In each simulated trial, we assumed that time to event of interest (neurologic death) and time to competing risks (non-neurologic death) were independently and exponentially distributed according to the true hazard rates specified in Section 14.3.3. We assumed that 333 patients (based on the Pintilie formula) were accrued uniformly over 33 months with 12 months of additional follow-up after accrual completion. An interim futility test was performed at the designated 1-sided significance level when 64 events of interest have occurred. If the simulated trial did not stop early due to futility, then the trial proceeded to full accrual and a final efficacy analysis was conducted when 127 events of interest has been reached based on a 1-sided 0.05 level test. Under the null hypothesis (when HA-WBRT does not prolong time to neurologic death as compared to SRS), we recorded the following design characteristics: (i) the probability of early stopping due to futility, (ii) timing of futility analysis (since trial activation), (iii) number of patients enrolled by the time of interim analysis, (iv) estimated cause-specific hazard ratio and 95% CI at time of interim analysis based on Cox proportional hazards model, and (v) the probability that the trial continues to full accrual and rejects the null hypothesis (this is the overall type I error). Under the alternative hypothesis (when HA-WBRT prolongs time to neurologic death as compared to SRS), we recorded the following design characteristics: (i) the probability of early stopping due to futility, (ii) timing of final efficacy analysis since study activation (among trials that proceed to full accrual), (iii) the estimated cause-specific hazard ratio and 95% CI based on Cox proportional hazards model (among trials that proceed to full accrual), and (iv) the probability that the trial continues to full accrual and rejects the null hypothesis (this is the power of the design).

The table below displays the operating characteristics of the study design incorporating the proposed futility monitoring rule in the context of this trial. Balancing the desire between maximizing the probability of stopping the trial early under the null and minimizing the power loss, we selected the 1-sided significance level of 0.40 for the interim futility test. With this rule, the trial will have on average 60% of the chance to stop at interim under the null hypothesis. At the same time, there is approximately 33% (median 111 patients) saving in sample size if the trial stops early. This design is only associated with a negligible power loss (~2%) as a result of the futility test. Based on the simulations, the median time for the futility analysis to occur would be roughly 28 months after study activation (including the initial 6-months ramp-up). The overall type

I error is maintained at under the 5% nominal level (4.5%). As expected, the median estimated cause-specific HR was 1.0 (95% CI: 0.61-1.64) under the null hypothesis. Under the alternative hypothesis, the design will have only 5.2% of the chance to stop at the futility interim. The median estimated cause-specific HR was 0.61 (0.43-0.87). The final efficacy analysis (if the trial does not stop early at interim) will occur roughly 51 months after study activation (again including the initial 6-months ramp-up).

The results of the interim analyses will be reported to the NRG Oncology DMC, along with all other information described earlier. The NRG Oncology statistician will provide a provisional recommendation to the DMC, who will deliberate and ultimately render a recommendation regarding actions on the trial to the NRG Oncology Group leadership.

Operating Characteristics of the Study Design

1-sided sig. level at interim	Under Null Hypothesis					Under Alternative Hypothesis			
	prob. Of stopping at futility	median HR (95% CI) at interim analysis	median # pts enrolled by time of interim (range)	median time (month) of interim since study activation (range)	type I error	prob. Of stopping at futility	median HR (95% CI) at final analysis	median time (months) of final analysis since study activation (range)	power
0.30	71%	1.0 (0.61-1.64)	221 (169-285)	28 (23-35)	4.5%	9.2%	0.60 (0.42-0.86)	50 (39-134)	81.4%
0.40	60%	1.0 (0.61-1.64)	221 (163-282)	28 (22-35)	4.5%	5.2%	0.61 (0.43-0.87)	51 (39-141)	82.7%
0.50	50%	1.0 (0.61-1.64)	220 (162-278)	28 (22-34)	4.8%	3.2%	0.62 (0.43-0.88)	51 (39-194)	83.7%

14.5 Accrual/Study Duration Considerations

For the recent NRG phase III trial (NRG-CC001) evaluating the role of WBRT for brain metastases, the expected accrual rate was 9 patients per month over 5 years. In actuality, the trial accrued at a rate of 16.2 patients per month and completed accrual in 32 months, 2 years sooner than expected. Based on the historical experience of accrual to NRG brain metastasis trials, we anticipate negligible accrual during the first 6 months while sites obtain IRB approval and activate the trial. Thereafter, we expect a uniform accrual rate of 10 patients per month. This estimate is based on observation that the BMV ≥ 4 cohort comprises approximately 60% of brain metastasis patients. The required number of neurologic death events for the primary endpoint is expected to be reached about 12 months after accrual completion. It is projected that the primary analysis will take place approximately 12 months after accrual completion or 51 months after study activation (6 months ramp-up + 33 months accrual + 12 months additional follow-up).

If the trial is stopped early due to futility in the experimental arm, patients remaining on study treatment who are felt to be benefiting may continue at the discretion of the treating investigator in discussion with the patient and a revised written informed consent form that will be generated as needed.

14.6 Secondary Objectives Study Endpoints (06-APR-2023)

14.6.1 Secondary Hypotheses and Endpoints:

Endpoints for the secondary objectives of this trial include OS, intracranial progression-free survival, brain metastasis velocity at subsequent relapse, summary statistics on adverse event frequencies, the MDASI-BT, EQ-5D-5L, PROMIS cognitive function patient-reported outcome (PRO) measures, neurocognitive function (NCF) measures, and number of salvage procedures and estimated cost of brain-related therapies. The following hypotheses will be evaluated:

- To determine if HA-WBRT in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year prolongs overall survival as compared to SRS.
- To evaluate if HA-WBRT in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year prolongs intracranial progression-free survival as compared to SRS.
- To evaluate if HA-WBRT in patients distant brain failure with brain metastasis velocity ≥4 new brain metastases/year improves brain metastasis velocity at subsequent relapse as compared to SRS.
- To assess perceived difficulties in cognitive abilities, symptom burden and health status, as measured by the MDASI-BT, EQ-5D-5L and PROMIS cognitive function, after HA-WBRT, as compared to SRS, in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year.
- To compare neurocognitive function outcomes following HA-WBRT, as compared to SRS, in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year.

- To tabulate and descriptively compare the post-treatment adverse events associated with the interventions.
- To compare the number of salvage procedures in patients who receive HA-WBRT, as compared to SRS, in patients with distant brain failure with brain metastasis velocity ≥4 new brain metastases/year.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Intracranial Progression-Free Survival

Intracranial progression-free survival (IPFS), defined as time from randomization to intracranial progression or death from any cause, will be evaluated among all trial participants. Analysis for this endpoint will consist of estimation of the IPFS curves via the Kaplan-Meier method and a stratified log-rank test. Additional analyses may consist of estimating the hazard ratio via the Cox proportional hazards model, accounting for other prognostic covariates (and evaluating whether the proportional hazards assumption holds or whether any treatment effect is notably time-varying), and evaluating for potential treatment by prognostic covariate interactions.

Overall Survival

Overall survival (OS) is defined as time from randomization to death from any cause. The analytical techniques for OS would be similar to those for IPFS, as described above.

Adverse Events

Adverse events (AEs) will be graded according to CTCAE v5.0. Comprehensive summaries of all Aes by treatment arm will be generated and examined. Counts and frequencies of worst (highest score) AE per patient will be presented overall and by AE type category, separately by assigned treatment group. The proportion of patients with at least one grade 3 or higher AE will be compared between treatment arm. Similarly, frequencies for specific potentially treatment related Aes where grade 3 or higher events are noted may be compared. Any frequencies to be tested will be evaluated using the chi-square or exact test as appropriate, with two-sided significance level 0.05. It noted that no hypotheses are specified regarding expected differences in AE frequency, and that power can be high for frequency tables with large sample size; only clinically material differences that represent potential patient risk will be of interest.

Neurocognitive Function

As described in Sections 2.4 and 11.1, neurocognitive function (NCF) will be assessed using the Hopkins Verbal Learning Test – Revised (Benedict 1998), Trail Making Test (Tombaugh 2004), and the Controlled Oral Word Association test (Ruff 1996). These widely used and standardized psychometric instruments have been shown to be sensitive to the impact of cancer and the neurotoxic effects of cancer treatment in other clinical trials (Gilbert 2014; Meyers 2004; Wefel 2011). The tests have published normative data that account for age and, where appropriate, education and gender. The NCF assessments will be administered according to the schedule described in Section 4.

The established metric for clinically-significant change is the Reliable Change Index

(RCI; Jacobson 1991). The RCI is derived from the standard error of measurement of each test and represents the 90% confidence interval for the difference in raw score from baseline to the next assessment that would be expected if no real change occurred:

RCI = 1.64(standard error of difference), where standard error of difference
= $[2(\text{standard error of measure}^2)]^{1/2}$, and standard error of measure
= standard deviation$_1[(1 - r_{xy})^{1/2}]$

This yields the following RCI values for each test in the Clinical Trial Battery:

NCF Test	RCI Value
HVLT-R Total Recall	5
HVLT-R Delayed Recall	3
HVLT-R Delayed Recognition	2
TMT Part A	12
TMT Part B	26
COWA	12

At each assessment, change in raw test score relative to baseline are calculated, and declines in a score that meets or exceeds the RCI value is categorized as a failure. **Cognitive failure (CF)** is defined as a decline on at least one of the Clinical Trial Battery tests (HVLT-R, TMT, COWA) that meets or exceeds the RCI value.

We have chosen to prioritize the primary NCF/QOL analysis to include changes within the first 12-month time period because we expect to see the most meaningful effects on cognitive function during the first year after randomization. As such, patients will complete NCF testing at baseline, month 2, month 4, month 6, month 9, and month 12. The key objective for the NCF analysis is to compare the **cognition failure neurologic death free survival (CFNDFS)** between the two treatment arms. CFBNDFS is defined as the duration from randomization to time of CF or neurologic death, whichever comes first. Detailed definition of neurologic death, the primary efficacy endpoint of the parent trial, is given in Section 4. The primary comparison of treatment effect on CFNDFS will be based on a 1-sided 0.05-level test for cause-specific hazard ratio (CHR) in a Cox proportional hazards model. A 1-sided test is selected because our hypothesis is that HA-WBRT will improve cognitive outcomes as compared with SRS.

Participation in the real time integrated neurocognitive function study is mandatory for all patients that are proficient in English and French-Canadian, given that the psychometric properties for translated tests are either not known or not as robust. Thus, we very conservatively estimate at least 70% of patients will be eligible and evaluable for the primary endpoint of CFNDFS (with exception of patients who are not English or French-Canadian speaking (~2-5%), early withdrawal of consent, lack of follow-up, or refusal to participate, etc.) but there could be as high as 90% of the full trial population. We assume that 6-month cognitive failure (CF) rate in the SRS arm is 30%, which translates to 12-months CF rate of 51% assuming exponential distribution. In BN009, we assume that 12-month neurologic death rate in the SRS arm is 34%. Combining CF and neurologic death as in the CFNDFS definition, it is estimated that about 85% of patients

in the SRS arm will have experienced a CFNDFS event by 12 months after randomization (corresponding to a hazard rate of 0.158 in the SRS arm). We expect that HA-WBRT will improve 12-month CFNDFS rate by 10% (i.e. from 15% to 25%). This difference translates to a hazard ratio (HA-WBRT vs. SRS) of 0.73. Assuming uniform accrual of 33 months with an additional follow-up of 12 months after accrual completion, the following table describes the percentage of patients evaluable for the CFNDFS, the effective sample size, expected number of CFNDFS events by the end of the trial, and statistical power to detect the hypothesized effect size, using a 1-sided 0.05 level test, assuming the percentage of patients evaluable for the CFNDFS primary endpoint ranges between 70% and 90%. Note that the timing of this analysis will be based on the timing for primary analysis of BN009, and will take place roughly after all participating patients have at least 12 months of follow-up.

Percentage of patients evaluable for CFNDFS endpoint	Effective sample size evaluable for CFNDFS endpoint	Estimated number of CFNDFS events by the end of the trial	Power to detect hypothesized effect in CFNDFS (HR = 0.73)
70%	233	222	75%
80%	266	254	80%
90%	300	286	84%

As a secondary analysis, the cumulative incidence function estimator will be used to estimate the median time to cognitive failure or neurologic death (CFND) in the presence of precluding non-neurologic deaths (Korn and Dorey 1992). Gray's test will be used to test for a statistically significant difference in the distribution of CFND (Gray 1988). Results will be interpreted in light of competing non-neurologic deaths, which may be frequent. Finally, as an exploratory analysis, we will assess the change in NCF scores over time. Specifically, we will implement mixed effects models for repeated measures to evaluate NCF scores longitudinally. Mixed effects models describe the rate of change in scores over time for each treatment arm (fixed effect), taking into account the between-patient variability by incorporating each patient's individual starting point and individual rate of change (random effect) into the model. The NCF scores will be the dependent variables in these models. Independent variables will include time, study arm, baseline stratification factors, and the interaction between time and study arm. An unstructured correlation matrix will be used to model the correlation between repeated observations. Of particular interest is the treatment group by time interaction effect, representing a difference in cognitive function experience over time among patients in the two groups.

Patient-Reported Outcomes

MDASI-BT: As described in Section 11.2, symptom burden will be assessed using the MDASI-BT-modified (Armstrong 2006). The MDASI-BT consists of 23 symptoms rated on an 11-point ordinal scale (0 to 10) to indicate the presence and severity of the symptom in the last 24 hours, with 0 being "not present" and 10 being "as bad as you can imagine." Symptoms included on the instrument are those commonly associated with cancer therapies and those associated with neurologic and cognitive symptoms associated with the tumor itself. The MDASI-BT also includes ratings of how symptoms (on 0-10 scale)

have interfered with different aspects of the patient's life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The MDASI-BT will be administered according to the schedule described in Section 4.

We will conduct a longitudinal analysis that will focus on patterns of score change over time points (baseline, month 2, 4, 6, 9, and 12) in MDASI-BT. It is posited that patients in the HA-WBRT arm will achieve greater control of brain metastasis which may lead to more favorable outcomes with respect to symptoms burdens. To assess this, we will implement mixed effects models for repeated measures to evaluate the MDASI-BT scores longitudinally. Mixed effects models describe the rate of change in scores over time for each treatment arm (fixed effect), taking into account the between-patient variability by incorporating each patient's individual starting point and individual rate of change (random effect) into the model. The MDASI-BT scores will be the dependent variables in these models. Independent variables will include time, treatment arm, baseline stratification factors, and the interaction between time and treatment arm. An unstructured correlation matrix will be used to model the correlation between repeated observations. Of particular interest is the treatment group by time interaction effect, representing a difference in symptom burden experience over time among patients in the two groups.

To control for multiple comparisons among time points, a hierarchical analytic approach described below will be undertaken:

a) Perform an overall (omnibus) test of the treatment group by timepoint interaction effect. Prior to this test, model characteristics, including trajectories of scores may be examined via regression diagnostics within treatment arm, and appropriate functional form for the models then specified.
b) If an overall difference in score trajectories by arm is confirmed, then
    a. test timepoint-specific differences between arms
    b. characterize treatment-arm specific patterns over time within the group treatment groups (changes from baseline, shape of the trajectory, etc.)
c) If overall differences by arm cannot be established, then exploratory characterizations of the symptoms experience will be undertaken within each treatment arm, separately.

PROMIS Cognitive Function Short Form 4a v2.0: This measure is a 4-item questionnaire that assesses patient-perceived cognitive concerns over the past 7 days. The 4-item short form was found to be highly correlated with the full 8-item measure and demonstrated excellent internal consistency reliability and has criterion validity related evidence for measuring cognitive concerns but not cognitive performance. This measure asks the patient to rate the frequency of the following cognitive complaints over the preceding 7 days: (1) My thinking has been slow; (2) It has seemed like my brain was not working as well as usual; (3) I have had to work harder than usual to keep track of what I was doing; and (4) I have had trouble shifting back and forth between different activities that require thinking. Each question has five response options ranging in value from one to five (with lower scores indicating more severe cognitive concerns). The total raw score for a short

form would be the sum of the values of the response to each question (therefore, for a short form which all questions are answered, the lowest possible score is 4 and the highest possible raw score is 20). Similar longitudinal analytic strategy as outlined above for MDASI-BT will be adopted to analyze the PPOMIS Cognitive Function data.

EQ-5D-5L: The EQ-5D-5L is a standardized self-report measure of health status. The 5-level EQ-5D version (EQ-5D-5L) was introduced by the EuroQol Group in 2009 to improve the instrument's sensitivity and to reduce ceiling effects, as compared to the EQ-5D-3L. It consists of 2 pages, the EQ-5D-5L descriptive (mobility, self care, usual activities, pain/discomfort, anxiety/depression) using 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems) and the EQ visual analogue scale (EQ VAS). The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. We will employ similar longitudinal analytic strategies as delineated above for MDASI-BT to analyze EQ-5D-5L data.

Missing Data Considerations for PRO and NCF Studies

A certain degree of attrition from the NCF/PRO studies, due to both patient refusal or other reasons for missed assessments, and deterioration due to disease, is expected. Characteristics of patients with missing data will be evaluated to identify imbalance in factors such as treatment, baseline scores, and other clinical and demographic features. Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 2010, Verbeke 2000). If missing data are MCAR or MAR, then a mixed model using maximum likelihood is sufficient because all available data can be used. A joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

For NCF testing, all standard monitoring procedures will be applied to monitoring and ensuring patients complete NCF testing at the prespecified time points. Noncompliant sites will be contacted and reminded that this is a mandatory component of the trial. NRG HQ will send reminder emails to sites for each patient a week in advance of their scheduled follow up tests time point to help reduce missing data. The trained and certified test administrator selects a test completion code for every test with every patient indicating the test was completed or the reason a test was not completed or was discontinued such as discontinued due to the severity of neurologic disability.

Power Calculations

In this trial, the symptom burdens and patient-perceived cognitive functions will be assessed with MDASI-BT, PROMIS Cognitive Function Short Form 4a v2.0, and EQ-5D-5L instrument. The expected difference in symptom burdens and cognitive functions between treatment arms will partly depend on relative disease control benefit as well as

the adverse events between two treatment arms. Of key interest is the difference in change in symptom burden and cognitive function from baseline to 6 months (from the start of treatment) between the two treatment arms. While scales for the individual instrument questions are quantitative, they represent ordinal values on a bounded range rather than continuous quantities. Nonetheless, in aggregate these scores approximate continuous distributions, and appropriate transforms will be applied to improve consistency with model assumptions for the outcome measure. Note that the meaningful effect size for these tools is still in debate. Cohen's widely used rules of thumb for interpreting the magnitude of difference define 0.8 standard deviation (SD) as a "large" effect size, 0.5 SD as a "medium" effect size, and 0.2 SD as a "small" effect size (Cohen 1988). Effect size below 0.5 SD, supported by data regarding the specific characteristics of a particular quality of life assessment or application, may also be clinically meaningful (Sloan 2005). Assuming 266 patients (roughly 80% of the patients enrolled in the treatment trial; equally split between two arms) will participate in the QOL studies and have both baseline and 6-month follow-up data, each study will have 80% statistical power to detect effect size (mean difference between arms / standard deviation) of 0.35 or greater using a 2-sided 0.05 level t-test.

14.7 Exploratory Hypothesis and Endpoints

Brain metastasis velocity at subsequent distant brain relapse (BMVs)
BMVs will be defined as follow:

> BMVs = (total number of new brain metastases since on-study SRS) / (years since on-study SRS),

where on-study SRS refers to the SRS procedure that the patient received on this study.

The Wilcoxon rank-sum test will be used to compare the distributions of BMVs between the two treatment arms at 2-sided 0.05 level.

Radiographic endpoints
We will collect baseline and follow-up MR imaging axial T2 FLAIR (PREFERRED) or T2 volumes and extract imaging data from both the SRS and HA-WBRT +SRS arms. The entire MRI DICOM data will be stored at baseline and month 4. We will extract first order geometric features. For the geometric features we will use axial T2 FLAIR (PREFERRED) or T2 imaging sequence. The scanning parameters are available on the ADNI website as described in Section 5.2. Quality control on image acquisition is to be provided by IROC Philadelphia imaging QA center to ensure consistent image quality across different scanners. The imaging sets will be standardized to account for inter-scanner variability by using bias field correction, anisotropic diffusion noise reduction and signal intensity normalization. The whole brain volume, white matter volumes and volume of metastatic disease will be segmented by two independent investigators using a single software system.

We will evaluate the dose to these structures and determine if pre-treatment white

matter volume may be correlated with cognitive function (HVLT-R) and patient reported difficulties in cognitive abilities (PROMIS-4a v2.0). Specifically, changes in score of cognitive assessments will be calculated by subtracting the score at the 4-month follow-up from the baseline score. For HVLT-R, a positive change score would reflect a cognitive decline, whereas a negative score would indicate decline for PROMIS-4a v2.0. The Pearson's correlation will be estimated to characterize the association between imaging features (whole brain volume, white matter volumes and volume of metastatic disease) and change in cognitive score, both within two treatment arms separately as well as combining data across arms. In the event that normality assumption may be violated, rank-based correlation coefficients such as Spearman or Kendall will be used. At the present time, there is a paucity of literature data suggesting that imaging biomarkers in this disease will be "predictive" of benefit from SRS alone in preserving cognitive function. However, the imaging data generated from this trial would provide an unique opportuntity to explatory this hyopthesis. Specifically, we will also explore via a Cox proportional hazards model the presence of a statistical interaction between these imaging parameters and treatment group based on 2-sided 0.05 level test. Of note, given the limited sample size (projected to be ~100 patients based on RTOG 0933 experience) available for the imaging obejcteives, it is appreciated that statistical power for the interaction test is likely very limited (Polley 2013). As such, these analyses will be hypothesis-generating in nature.

A secondary analysis of RTOG 0933 using HA-WBRT demonstrated a correlation between MRI axial T2/FLAIR (PREFERRED) volume and cognitive outcomes (Bovi 2019). In that study, about 29% of the patients (33/113) had pre-treatment postcontrast volumetric T1 and axial T2/fluid-attenuated inversion recovery MRI and underwent pre-treatment and 4-month post-treatment cognitive testing. This trial will randomize a total of 333 patients. Assuming the same percentage of patients evaluable for the imaging objective as the Bovi et al. study, the sample size for this aim would be about 97 patients. Assuming a two-sided 0.05 level test of correlation, this sample size would allow us to detect a true correlation of 0.28 or larger with 80% statistical power.

14.8 Gender/Ethnicity/Race Distribution

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	2	1	0	0	3
Asian	3	1	0	0	4
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	26	9	0	0	35
White	157	114	5	4	280

More Than One Race	0	0	0	0	0
Total	188	125	5	4	322

Racial Categories	**INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	1	0	0	3
White	14	10	1	0	25
More Than One Race	0	0	0	0	0
Total	16	11	1	0	28

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APPENDIX I (06-APR-2023)
Medidata Patient Cloud ePRO Operational Instructions

Introduction
Electronic collection of patient-reported outcomes (ePRO) through Medidata's Patient Cloud mobile ePRO application is preferred but not mandatory. Patients who will be submitting PRO data via the Patient Cloud mobile app must be registered to the ePRO application by an authorized site staff after the patient has been registered to the study. Patients may use their own mobile device or one provisioned by the site.
Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to the Patient Cloud (ePRO) mobile app with their passwords or their PIN codes on the same device.

Patient Cloud mobile ePRO Application Download
Note that there are multiple versions of the Patient Cloud mobile ePRO app. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error upon logging into the Patient Cloud mobile ePRO app if the wrong version is downloaded. **This protocol is using the current version named "Patient Cloud" with the following logo:**

CRA Site Users
Site staff require access to the ePRO application. This access is granted through iMedidata, and is similar to the process of obtaining access to Rave studies. Site staff will receive an invitation to the ePRO application which they must accept in order to begin registering patients. Staff that have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Medidata Account Activation and Study Invitation Acceptance instructions are located on the CTSU members' website under Resources >Frequently Asked Questions (FAQs)>Rave>1. How do I gain access to iMedidata and studies in Rave>Medidata Account Activation and Study Invitation Acceptance. Site staff will not be able to access the study in the ePRO application until all required Rave and study specific trainings (eLearnings assigned in iMedidata) are completed.
Additional information on iMedidata/Rave is available on the CTSU members' website under the *Data Management tab* and further under the *Help* button or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

CRA Instructions for Preparing a Site Device
Sites conducting studies entirely on-premises, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to the Patient cloud mobile app with their passwords or their PIN codes on the same device. If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the Patient Cloud mobile ePRO app to the device and set the mobile app to multi-user mode if applicable. *Note only 1 version of the mobile app is active per protocol. This protocol is using the version named simply "Patient Cloud" with the cloud and dot logo.*

To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Under **Mode**, then select **Multi-User** from the drop-down menu.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

Patient Users

To use the ePRO mobile app, patients will need to use their own device (Apple/iOS or Android smartphone or tablet) or one provided by the site.

In both cases, short-term data will only appear on the device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and data will no longer be visible on the device.

Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

Quick Reference Cards (QRCs) are available to download, print for use by the site, and to hand out to the patient if desired. The QRCs can be found here (staff iMedidata login is required for access) and include: Patient Cloud iOS App Download, Account Activation with Email and Password, Account Activation with Multiple Studies Using Existing Email Address, and Troubleshooting.

Downloading the Patient Cloud mobile ePRO App

If you are using your personal device, and you do not have the Patient Cloud mobile app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the smart phone or tablet onto which you intend to install the mobile app. If the correct version (see logo below) of the Patient Cloud mobile app is already on the device, or if you are using a provider's device, you can skip this section. There are multiple versions of the Patient Cloud mobile app available. Ensure that the correct version of the Patient cloud mobile app is downloaded. *Note only 1 version of the mobile app is active per protocol. This protocol is using the version named simply "**Patient Cloud**" with the cloud and dot logo.*

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

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

For iOS (Apple iPhones and iPads):

1. An Apple ID is required for downloading the Patient Cloud mobile ePRO app.

2. Tap the *App Store* icon on your mobile device.
3. Search "**Patient Cloud**" for the appropriate ePRO mobile app, download the one with the cloud logo shown and follow the installation instructions.

For Android smart phones and tablets:

1. A Google account is required for downloading the ePRO mobile app
2. Tap the *Play Store* icon on your mobile device.
3. Search "**Patient Cloud**" for the appropriate ePRO mobile app, download the one with the logo shown and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the ePRO mobile app.
Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

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

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

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

Logging in to the Patient Cloud (ePRO) mobile app

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

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

Setting a PIN Code

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

time you need to log in to the ePRO mobile app. Instead, you can enter a four-digit PIN.

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

If you forget your PIN code, tap "**Forgot your PIN?**" and you can access the app using your email and password. You may reset your PIN by tapping the **options menu** (three vertical dots) on the top right of most pages (after login) and selecting **Set PIN**.

Resetting Your Password

You can reset your password by using the options menu (three vertical dots) on the top right of most pages (after login).

1. Tap the **options menu icon** (three vertical dots).
2. Tap ***Reset Password***.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

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

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

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

To complete and submit form(s):

1. Select the appropriate form.
   Follow the on-screen instructions until you reach the end of the form where you may be given the opportunity to review and change your responses prior to submitting.

2. If given the opportunity to review and update, review your responses by scrolling down the list; if you need to change an answer, tap the question to go back and change the answer.

3. When you are ready to submit, tap Submit Your Data.

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

Patient Compliance
The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

Security
All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.
The data will only reside on the device for a short period of time. Once the user clicks "Submit," the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The patient's email links the device (used) and (ePRO) account to where the data is stored. The patient's email is not visible to anyone in the system.
The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.
The ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).
Messages and information communicated to and from the Patient Cloud are encrypted and therefore this information cannot be read if intercepted while in transit.

Site checklist for activities prior to consenting a patient

- Accept study invitation at iMedidata.com
    - Site staff must be rostered in RSS and have received an invitation to the ePRO application
- Site staff must have already completed required eLearning assigned in iMedidata for the ePRO application before gaining access to the study in Rave. Contact the LPO to request appropriate Rave access to register patients in the ePRO application.
- Verify the IOS or Android operating system is using the most current version
- Verify that the correct Patient Cloud mobile ePRO app is being used. Note only 1 version of the mobile app is active per protocol. This protocol uses the current version named "Patient Cloud" with the cloud and dot icon (see below).
- If using institutional shared devices, for the first patient only: Verify the ePRO mobile app is in Multi-User mode.

Note: Sites should consider copying this site checklist and placing it in the clinic or area where site is consenting patients to ePRO and also copy the correct name ("Patient Cloud") and image of the ePRO mobile app version with it to help remind staff and patients of the correct version being used in the protocol. Sites should also inform patients that short term data will only appear on the device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and data will no longer be visible on the device.

Patient withdraws study consent or withdraws consent from participating on ePRO
CRA must instruct the patients that are participating on ePRO who decide to withdraw consent to delete the App from their smart phones. This will prevent QOL reminders from

being sent to the patient.

”””””””

APPENDIX II: MEMANTINE PILL DIARIES (06-APR-2023)

Today's Date _____/_____/_____ Patient Initials _____ Patient Study ID _____

MEMANTINE PILL DIARY

NRG-BN009

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

Twice Daily Dosing

INSTRUCTIONS TO THE PATIENT:

Dosing Schedule:

	Daily AM Dose	Daily PM Dose
Week 1	5 mg	None
Week 2	5 mg	5 mg
Week 3	10 mg	5 mg
Weeks 4-24	10 mg	10 mg

- Record the date, the dose and the time taken.
- If you forget dose and it has been less than 2 hours, you can take dose and document time taken. If it has been more than 2 hours please SKIP dose and note skipped dose on the diary. Resume with next scheduled dose. DO NOT take a double dose or try to make up any dose.
- If several doses in a row are missed, dosing may need to start over at lower doses and increased to higher doses. Contact the study team if this happens and document it in the pill diary.
- If you have any comments or notice any side effects, please record them in the Comments column.

Today's Date _____/_____/_____ Patient Initials _____ Patient Study ID _____

Week_____

Day	Date	AM Dose	AM Dose Time	PM Dose	PM Dose Time	Comment
1						
2						
3						
4						
5						
6						
7						

Patient's Signature: _____ Date: _____

Today's Date _____/_____/_____ Patient Initials _____ Patient Study ID _____

MEMANTINE PILL DIARY

NRG-BN009

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

Extended Release Dosing

INSTRUCTIONS TO THE PATIENT:

Dosing Schedule:

	Daily Dose Extended Release Memantine
Week 1	7 mg
Week 2	14 mg
Week 3	21 mg
Weeks 4-24	28 mg

- Record the date, the dose and the time taken.

  DO NOT take a double dose or try to make up any dose.

- If several doses in a row are missed, dosing may need to start over at lower doses and increased to higher doses. Contact the study team if this happens and document it in the pill diary.

- If you have any comments or notice any side effects, please record them in the Comments column.

Patient's Signature: _____ Date: _____

Today's Date _____/_____/_____ Patient Initials _____ Patient Study ID _____

Week _____

Day	Date	Dose	Dose Time	Comment
1				
2				
3				
4				
5				
6				
7				

Patient's Signature: _____ Date: _____

APPENDIX III: PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:
Diagnosis:
Study Doctor:
Study Doctor Phone #:
NCI Trial #:
Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX IV: SUMMARY OF KEY IMAGING REQUIREMENTS (06-APR-2023)

(1) What are the minimum MRI sequence requirements for the study?

- Axial T2 FLAIR (preferred) or T2
- 3D T1 Post-Contrast
- T1 Pre-Contrast

NOTE: FOR THE PRE-CONTRAST T1 IMAGINNG, 3D IMAGING SEQUENCE IS STRONGLY ENCOURAGED

(2) Regarding the 3D T1 MRI:

a. Both pre-contrast T1 and post-contrast T1 imaging are required. A 3-D imaging sequence is required for post-contrast T1 imaging and strongly encouraged for pre-contrast T1 imaging.

b. **Can I use a different sequence for pre- versus post-contrast?**
It is recommended that the 3D T1 be acquired as a matched data set pre- and post-contrast.

c. **Can the 3D T1 be acquired in the sagittal plane?**
If you have isotropic voxels, it is acceptable to acquire the 3D sequence in any plane.

(3) Regarding the axial T2 FLAIR (preferred) sequence:

a. Is axial acquisition required?
Yes, if 2D sequence is obtained.

b. Should the axial T2 FLAIR (preferred) or axial T2 be performed at an angle or straight?
These can be performed either straight or at a standard AC-PC clinical angle. If the pre gadolinium 3D T1 is acquired in an axial plane, then the axial T2 FLAIR (preferred) or axial T2 and post gadolinium 3D T1 sequences need to be set up the same way. Either straight or angled is acceptable for the study.

c. Can we use our site's standard 2D T2 FLAIR?
Yes, as long as the acquisition is axial.

d. Can we substitute 3D T2/FLAIR?
Yes, as long as you have isotropic voxels, it is acceptable to acquire the 3D sequence in any plane.

(4) Is 2D Spin Echo T1 post-contrast required?
No.

(5) What MRI Brain imaging sequences are to be submitted through TRIAD?
The entire Diagnostic brain MRI exam is to be submitted for all enrolled subjects. Please understand this means, the three required MRI brain sequences (3D post T1, pre T1 (3D imaging sequence strongly encouraged), and axial T2 FLAIR and/or axial T2 FSE), as well as all other sequences obtained for the brain MRI visit. Please also submit ADC and DWI imaging if available. **These sequences should be submitted under timepoint "Baseline" separately from RT "Baseline" so that they properly credit**

in the Medidata Rave system.

Minimum standard MR imaging protocol as per Kaufmann et al. Please consult Kaufmann et al (2020) for more details.

	3T MRI (Preferred)				1.5T MRI			
	3D T1 Pre[a]	3D T1 Post[b]	Ax 2D T2/FLAIR[c,i]	Ax 2D T2[c]	3D T1 Pre[a]	3D T1 Post[b]	Ax 2D T2/FLAIR[c,i]	Ax 2D T2[c]
Sequence	IR-GRE[d]	IR-GRE[d]	TSE[e]	TSE[e]	IR-GRE[d]	IR-GRE[d]	TSE[e]	TSE[e]
Plane	Sagittal or Axial	Sagittal or Axial	Axial	Axial	Sagittal or Axial	Sagittal or Axial	Axial	Axial
Mode	3D	3D	2D	2D	3D	3D	2D	2D
TR (ms)	2100[f]	2100[f]	>6000	>2500	2100[f]	2100[f]	>6000	>3500
TE (ms)	Min	Min	100-140	80-120	Min	Min	100-140	80-120
TI (ms)	1100[g]	1100[g]	2000-2500[h]		1100[g]	1100[g]	2000-2500[h]	
Flip angle	10°-15°	10°-15°	90°/≥160°	90°/≥160°	10°-15°	10°-15°	90°/≥160°	90°/≥160°
Frequency	256	256	≥256	≥256	≥172	≥172	≥256	≥256
Phase	256	256	≥256	≥256	≥172	≥172	≥256	≥256
NEX	≥1	≥1	≥1	≥1	≥1	≥1	≥1	≥1
FOV	256 mm	256 mm	240 mm	240 mm	256 mm	256 mm	240 mm	240 mm
Slice thickness	1 mm	1 mm	3mm	3mm	≤1.5 mm	≤1.5 mm	≤4 mm	≤4 mm
Gap/ spacing	0	0	0	0	0	0	0	0
Other options								
Parallel imaging	Up to 3x	Up to 3x	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Up to 2x

Abbreviations: TR=repetition time TE: echo time TI: inversion time
NEX: number of excitations FOV: field of view

[a]Pre-contrast T1 imaging is required and strongly encouraged to be acquired as a 3D imaging sequence with equivalent parameters to the 3D post-contrast T1 imaging.

[b]3D post-contrast T1 imaging is required.

[c]Axial T2/FLAIR or T2 sequence is required. Axial T2/FLAIR is strongly preferred.

[d]IR-GRE: inversion-recovery gradient-recalled echo sequence is equivalent to MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) and the inversion recovery spoiled gradient-echo (IR-SPGR or FAST SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba). A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.

[e]TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; Hitachi, Toshiba)

[f]For Siemens and Hitachi scanners. GE, Philips and Toshiba scanners should use a TR = 5-15 ms for similar contrast.

[g]For Siemens and Hitachi scanners. GE, Philips and Toshiba scanners should use a TI = 400-450 ms for similar contrast.

[h]Choice of TI should be chosen based on the magnetic field strength of the system (e.g., TI = 2000ms for 1.5T and TI = 2500ms for 3T).

[i]3D FLAIR is an optional alternative to 2D FLAIR with sequence parameters as follows per EORTC guidelines:

3D TSE/FSE acquisition; TE = 90-140ms; TR = 6000-10,000ms; TI = 2000-2500ms (chosen based on vendor recommendations for optimized protocol and field strength); GRAPPA≤2; Fat Suppression; Slice thickness ≤1.5mm; Orientation Sagittal or Axial; FOV ≤250mm x 250mm; Matrix ≥244x244.

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MRI: Brain
Version 1.02, 10Jun2021

Image quality in the multicenter setting can be greatly influenced by variances in acquisition protocols. These variances may be related not only to equipment manufacturer and model, but also technique.
The study may permit imaging per institutional standard-of-care. However, aligning image acquisition to established standards is essential for robust quality data.
The table below is provided as a guideline and overview for MRI Brain exams at either 1.5T or 3T. Please refer to your site's specific MRI manufacturer's imaging protocols for the optimal scanning protocol.
The Brain Tumor MRI examination should contain, at a **minimum**, the following sequences but not limited to:

1. Localization scan
2. Axial 3D T1 ***Pre-Contrast***
3. Axial T2 FLAIR
4. Axial 3D T1 ***Post Contrast*** (parameters and images should match the Axial 3D T1 pre-contrast)

   Advanced imaging sequences are frequently used such DWI, post contrast Axial T2 for tissue quantification (prior to Axial 3D T1 *post contrast*), and DSC.

Exam and Patient Preparation

Magnet Strength	1.5T or 3T	
Coil	Vendor Head Coil	
FOV	2D Sequences = 256 mm x 256 mm 3D Sequences = 240 mm x 240 mm	Adjust to patient body.
Patient Position	Supine	Position head as straight as possible and immobilize for a good quality scan.
Contrast Injection	Dual-chamber power injector recommended Contrast Bolus = 0.1 mmol/kg body weight Bolus Rate = 3-5 mL/s Saline Flush = 20 mL	Insertion of intravenous catheter in upper extremity prior to the start of imaging.
Slice Plane	Axial/Coronal/Sagittal planes (orthogonal to area of interest)	Scan direction based on site preference.

Image Acquisition

Localization Scan	3-plane localization scan	
Pre-Contrast Axial 3D T1w IR-GRE	<u>Siemens</u> Slice thickness ≤ 1.5 mm TR = 2100 ms TE = min TI = 1100 ms Flip angle = 10°–15° Acceleration = 2X <u>GE and Philips</u> Slice thickness ≤ 1.5 mm TR < 15 ms TE < min TI = 400–500 ms Flip angle = 10°–15° Acceleration = 2X	Must match Ax 3D T1 post contrast parameters and locations.
Pre-Contrast Axial T2 2D FLAIR	Orthogonal high-resolution Slice thickness = 3 mm Gap = 0 mm TR ≥ 6000 ms TE = 100–140 ms TI = 2500 ms (3T) = 1100 ms (1.5T) Flip angle = 90–160° Acceleration up to 2X	3D T2 FLAIR is acceptable as well.
Post-Contrast Axial 3D T1w IR-GRE	<u>Siemens</u> Slice thickness ≤ 1.5 mm TR = 2100 ms TE = min TI = 1100 ms Flip angle = 10°–15° Acceleration = 2X <u>GE and Philips</u> Slice thickness ≤ 1.5 mm TR < 15 ms TE < min TI = 400–500 ms Flip angle = 10°–15° Acceleration = 2X	Must match Ax 3D T1 post contrast parameters and locations.

Additional Image Acquisition

Axial 2D DWI (SS-EPI)	Slice thickness ≤ 4 mm Gap = 0 mm TR ≥ 5000 ms TE = min TI = 1100 ms Flip angles = 90°/180° Acceleration = up to 2X *b*-values = 0, 500, 1000 s/mm^2 Diffusion directions at least 3	Performed prior to contrast administration.
Ax 2D T2w	Slice thickness ≤ 4 mm Gap = 0 mm TR ≥ 2500 ms TE = 80–120 ms Flip angles = 90°/180° Acceleration = Up to 2X	Acquired post contrast and before postcontrast 3D T1-weighted images to control timing of images after contrast administration.
DSC	Slice thickness ≤ 3–5 mm Gap = 0–0.25 mm TR = 1000–1500 ms TE = 30–35 ms Flip angles = 60° Acceleration = Up to 2X	DSC is done post injection. Only the tumor needs to be covered, not the entire head.

References

1. ACR–ASNR–SPR Practice Parameter for the Performance and Interpretation of Magnetic Resonance Imaging (MRI) of the Brain, Res. 17 – 2019. https://www.acr.org/-/media/ACR/Files/Practice-Parameters/MR-Brain.pdf, accessed February 16, 2021.
2. Indications for MRI brain. https://mrimaster.com/index-3.html, accessed February 16, 2021.
3. MR Brain WO [contrast] Neuro Protocol. https://www.ohsu.edu/school-of-medicine/diagnostic-radiology/mr-brain-wo-neuro-protocol-0, accessed February 16, 2021.

APPENDIX V: DISEASE-SPECIFIC GRADED PROGNOSTIC ASSESSMENT (DS-GPA) (06-APR-2023)

For stratification, DS-GPA at time of enrollment will be used. DS-GPA is calculated using the following formula (Sperduto 2012):

Small Cell or Non-Small Cell Lung Cancer

	GPA Scoring Criteria			
Prognostic Factor	0	0.5	1.0	Patient Score
Age, years	>60	50-60	<50	
KPS	<70	70-80	90-100	
Extra-cranial mets	Present	---	Absent	
No. of brain mets	>3	2-3	1	
Sum total				

Melanoma

	GPA Scoring Criteria			
Prognostic Factor	0	1.0	2.0	Patient Score
KPS	<70	70-80	90-100	
No. of Brain Mets	>3	2-3	1	
Sum total				

Breast Cancer

	GPA Scoring Criteria					
Prognostic Factor	0	0.5	1.0	1.5	2.0	Patient Score
Age, years	≥60	<60	n/a	n/a	n/a	
KPS	≤50	60	70-80	90-100	n/a	
Subtype	Basal	n/a	LumA	HER2	LumB	
Sum total						

Renal Cell Carcinoma

	GPA Scoring Criteria			
Prognostic Factor	0	1.0	2.0	Patient Score
KPS	<70	70-80	90-100	
No. of Brain Mets	>3	2-3	1	
Sum total				

GI Cancers

	GPA Scoring Criteria					
Prognostic Factor	0	1.0	2.0	3.0	4.0	Patient Score
KPS	<70	70	80	90	100	
Sum total						