NRG ONCOLOGY

NRG-CC001
(ClinicalTrials.gov NCT #: 02360215)

A RANDOMIZED PHASE III TRIAL OF MEMANTINE AND WHOLE-BRAIN RADIOTHERAPY WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE IN PATIENTS WITH BRAIN METASTASES

This trial is sponsored by the National Cancer Institute (NCI) and will be led by NRG Oncology.

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A RANDOMIZED PHASE III TRIAL OF MEMANTINE AND WHOLE-BRAIN RADIOTHERAPY WITH OR WITHOUT HIPPOCAMPAL AVOIDANCE IN PATIENTS WITH BRAIN METASTASES

Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Memantine	Commercial	N/A	Exempt	N/A

Participating Sites

☒ U.S.
☒ Canada
☒ Approved International Member Sites

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A Randomized Phase III Trial Of Memantine and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Patients With Brain Metastases

SCHEMA

STEP 1: REGISTRATION

STEP 2: RANDOMIZATION

Baseline neurocognitive assessment: HVLT-R, TMT, COWA ***(required)***

NOTE: Neurocognitive assessments can be uploaded at the time of Step 1 registration.

STRATIFICATION

RPA Class: (see Appendix III)

1. Class I
2. Class II

Prior therapy:

1. None
2. Radiosurgery or surgical resection*

Arm 1

WBRT 30 Gy/10 fractions

+

Memantine**

Arm 2

WBRT with Hippocampal Avoidance using IMRT 30 Gy/10 fractions

+

Memantine**

*Radiosurgery or surgical resection within 8 weeks of Step 1 registration; otherwise stratify to None.

**Memantine to be administered during and after WBRT or WBRT with hippocampal avoidance for a total of 24 weeks.

OBJECTIVES

1.1 Primary Objective

Determine whether the addition of HA-WBRT increases time to neurocognitive failure at months 2, 4, 6 and 12 as measured by neurocognitive decline on a battery of tests: the Hopkins Verbal Learning Test-Revised (HVLT-R) for Total Recall, Delayed Recall, and Delayed Recognition, Controlled Oral Word Association (COWA), and the Trail Making Test (TMT) Parts A and B.

1.2 Secondary Objectives

1.2.1 Determine whether the addition of HA-WBRT preserves neurocognitive function at months 2, 4, 6 and 12 as separately measured by each test, the HVLT-R for Total Recall, Delayed Recall, and Delayed Recognition; COWA; and TMT Parts A and B.

1.2.2 Evaluate the potential benefit of HA-WBRT in symptom burden, as measured by the M. D. Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT)

1.2.3 Assessment of quality adjusted survival and health outcomesusing the EQ-5D-5L.

1.2.4 Compare cumulative incidence of progression and overall survival after WBRT versus HA-WBRT.

1.2.5 Compare adverse events between the treatment arms according to the CTCAE v4.0 criteria.

1.3 Exploratory Objectives (6/2/16)

1.3.1 Collect serum, whole blood, and imaging studies for future translational research analyses.

1.3.2 Evaluate MR imaging biomarkers of white matter injury and hippocampal volumetry at baseline and 6 months as potential predictors of neurocognitive decline and differential benefit from HA-WBRT as compared to WBRT.

1.3.3 Association of symptom burden and anxiety/depression with neurocognitive function

1.3.4 Evaluate the potential correlation between the prognostic scoring systems RTOG RPA and the diagnosis-specific graded prognostic assessment (DS-GPA) and neurocognitive function at baseline and overtime.

2 BACKGROUND

2.1 Rationale for Proposed Study

Neurocognitive Effects of Cranial Radiotherapy

Approximately 200,000 patients a year are treated with brain radiation for primary or metastatic brain tumors in the United States.(Robbins 2011) As recent advances in multi-modality therapy have led to improvement in survival for many cancer patients, more attention has been directed toward long-term treatment-related morbidity. Specifically, the effect of radiotherapy on the long-term cognitive performance of these patients is a major concern, as the morbidity can be devastating with a significant impact on both patient and caregiver quality of life (QOL).(Chien 2003; Laack 2004)

Brain metastases are the most common form of intracranial tumor in adults, with an annual incidence approximately 10 times greater than primary brain tumors.(Siegel 2012; De Vita 2001) Brain metastases are a significant cause of morbidity and mortality, occurring in approximately 20 to 40 percent of adult cancer patients (Nussbaum 1996) with an incidence as high as 200,000 cases per year in the U.S. alone.(Eichler 2007) It is expected the incidence of brain metastases will continue to increase due to improvement

in survival from systemic therapies.

Historically, patients with brain metastases had very limited survival of a few months. However, subgroups of patients exist in which prolonged survival is possible. A recursive partitioning analysis (RPA) of prognostic factors from Radiation Therapy Oncology Group (RTOG) brain metastases trials of 1200 patients from three consecutive RTOG trials found Karnofsky performance score (KPS) to be the strongest predictor of survival.(Gaspar 1997) RTOG 0614 treated 554 patients with whole brain radiotherapy (WBRT) but excluded patients with a KPS < 70 (i.e. RTOG RPA Class III).(Brown 2012) The median survival on this trial was over 7 months; by excluding poor performance status patients the study population was enriched with patients with an expected survival that was long enough to suffer the negative effects of WBRT.

Whole brain radiotherapy is the most common treatment for brain metastasis. Unfortunately, the majority of patients with brain metastases experience cognitive deterioration after WBRT. For example, a large trial prospectively evaluated patients with a battery of cognitive tests; by 6 months after WBRT 59% of patients had a greater than 2 SD decline in their performance in one or more tests.(Meyers 2004) RTOG 0614 prospectively tested brain metastases patients with a similar battery and found 80% of patients had evidence of cognitive deterioration 6 months after WBRT.(Brown 2012) With the high rate of cognitive decline over time and its impact on patient and caregiver QOL, it is imperative that interventions be developed to maintain cognitive function in this population over time.

Memantine and Prevention of Neurocognitive Toxicity

Glutamate is the principle excitatory amino acid neurotransmitter in cortical and hippocampal neurons.(Orrego 1993) One of the receptors activated by glutamate is the N-methyl-D-aspartate (NMDA) receptor, which is involved in learning and memory.(Danysz 1998) Ischemia can induce excessive NMDA stimulation and lead to excitotoxicity, suggesting that agents that block pathologic stimulation of NMDA receptors may protect against further damage in patients with vascular dementia.(Lancelot 1998) One such agent is memantine, an NMDA receptor antagonist. Memantine is a non-competitive, low-affinity, open-channel blocker that has been shown to be neuroprotective in pre-clinical models.(Chen 1997; Chen 1992; Pellegrini 1993) Additionally, in two placebo-controlled phase III trials, memantine proved to be a well-tolerated, effective treatment for vascular dementia, especially for patients with small-vessel disease.(Orgogozo 2002; Wilcock 2002)

The RTOG therefore launched a placebo-controlled, double-blind, randomized trial to evaluate the potential protective effect of memantine on neurocognitive function in patients receiving WBRT (RTOG 0614).(Brown 2012) Patients received WBRT and were randomized to receive placebo or memantine, 20 mg per day, within 3 days of initiating radiotherapy, for 24 weeks. Between March 2008 and July 2010, 554 patients were accrued of whom 508 were eligible. Patient and treatment characteristics were well balanced between arms. Grade 3 or 4 toxicities and study compliance were similar between arms. No differences in overall or progression-free survival were seen between

the arms. The memantine arm had significantly longer time to cognitive decline (HR 0.78; 95% CI, 0.62 to 0.99; p=0.02) and the probability of cognitive function preservation at 24 weeks was 30.6% in the memantine and 19.7% in the placebo arm. There was less decline on the Hopkins Verbal Learning Test-Revised Delayed Recall (HVLT-R DR) in the memantine arm (median decline of 0) compared to the placebo arm (median decline of 0.90) at 24 weeks (p=0.059) that was not statistically significant, as 149 analyzable patients at 24 weeks resulted in only 35% statistical power for the primary endpoint. There was less decline on the HVLT-R Delayed Recognition in the memantine arm at 24 weeks (p=0.0149) and the Mini Mental State Exam (MMSE) (p=0.0093). Fewer patients receiving memantine experienced decline on Controlled Oral Word Association (COWA) at 8 weeks (2% vs. 13% deterioration; p=0.0015). Linear regression models for the complete case data revealed significant differences favoring the memantine arm for COWA at 8 (p=0.008) and 16 weeks (p=0.0041) and for Trail Making Test (TMT) Part A and MMSE (p=0.0137 and 0.0038, respectively) at 24 weeks. Using the imputed data, the investigators found a significant difference for COWA scores at 8 weeks (p=0.0103) favoring the memantine arm.

In summary, the addition of memantine during and after WBRT resulted in better cognitive function over time—specifically delaying time to cognitive decline and reducing the rate of decline in memory, executive function, and processing speed. Although memantine showed evidence of better cognitive preservation after WBRT in patients with brain metastases, nearly 70% of patients still experienced cognitive deterioration by 6 months. With this high rate of cognitive deterioration it is imperative that additional interventions be developed to improve on the results achieved by memantine.

Rationale for WBRT with Hippocampal Avoidance

Evidence suggests that the pathogenesis of radiation-induced neurocognitive deficit may involve radiation-induced injury to proliferating neuronal progenitor cells in the subgranular zone of the hippocampus.(Mizumatsu 2003) It has been found that relatively small doses of radiation cause apoptosis in the subgranular zone of young rats and mice. .(Mizumatsu 2003; Gondi 2010) Clinical studies suggest that radiation-induced damage to the hippocampus plays a considerable role in the cognitive decline of patients. In particular, deficits in learning and memory observed in patients who have received cranial irradiation are thought to be related to hippocampal injury.(Abayomi 1996; Roman 1995) Thus there is interest in using advance radiation techniques such as intensity modulated radiotherapy (IMRT) to conformally avoid the hippocampal region during WBRT (HA-WBRT) to reduce the dose to the hippocampus, thereby putatively limiting the radiation-induced cognitive decline.

Feasibility of WBRT with Hippocampal Avoidance

Novel techniques have been developed to achieve HA-WBRT using linear accelerator (LINAC)-based IMRT delivery systems widely available at multiple academic and community radiation oncology practices.(Gondi 2010) RTOG 0933, a recently completed phase II trial of HA-WBRT for brain metastases, disseminated this knowledge and provided experience with these techniques. (Gondi 2013; Gondi 2014) In addition to

accruing 113 patients in 19 months at an accrual rate of 6 patients per month, this trial also built a technological infrastructure at RTOG to credential 113 physicians and 84 RTOG sites spanning community and academic institutions in the techniques of hippocampal contouring and HA-WBRT treatment planning.

WBRT with Hippocampal Avoidance and Prevention of Neurocognitive Toxicity

The primary endpoint of RTOG 0933 was mean relative decline in HVLT-R delayed recall score from baseline to 4 months, defined as follows Δ⟦HVLT⟧_ i=(⟦HVLT⟧_B-⟦HVLT⟧_F)/⟦HVLT⟧_B , where B=baseline and F=follow-up and a positive change indicates a decline in function. Based upon historical control data of 30% mean relative decline in HVLT-R delayed recall at 4 months compared to baseline in patients treated with WBRT without hippocampal avoidance, RTOG 0933 hypothesized that hippocampal avoidance during WBRT would lead to a 50% relative improvement over historical control, with a mean relative decline of 15% or less.

Analysis of RTOG 0933 demonstrates that the primary endpoint was highly significant, with a mean relative decline in HVLT-R delayed recall score from baseline to 4 months of 7.0% (95% confidence interval (CI): -4.7% to 18.7%), which was significant in comparison to the historical control (p=0.0003). The memory preservation benefit of hippocampal avoidance was maintained at 6 month follow-up, with a mean relative decline in HVLT-R delayed recall score from baseline to 6 months of 2.0% (95% CI: -9.2% to 13.1%). Similar preservation was also observed in the remaining HVLT-R domains. For instance, probability of HVLT Total Recall deterioration (defined as >5 point drop in Total Recall score from baseline to 4 months) after HA-WBRT was 19%. In comparison to the MD Anderson phase III trial of SRS with or without WBRT (Chang 2009), this result compared favorably to the 49% rate following SRS+WBRT. In addition to HVLT, RTOG 0933 included other assessments of verbal learning memory as well as visuo-perceptual and spatial learning and memory, both of which demonstrated no significant change from baseline following HA-WBRT. HA-WBRT was also associated with preservation of patient-reported quality of life, assessed using the Functional Assessment of Cancer Therapy and its validated brain subscale and the Barthel Activities of Daily Living.(Caine 2014)

Safety of WBRT with Hippocampal Avoidance

Following HA-WBRT on RTOG 0933, two grade 3 toxicities of fatigue and headache were observed; there were no grade 4 or higher toxicities. Of the 67 patients who developed progression, 3 patients (4.5%) experienced relapse in the hippocampal avoidance region with no difference in overall survival of these 3 patients compared to the 64 patients who did not relapse in the hippocampal avoidance region (i.e. 4 month median survival for each cohort of patients developing intracranial progression). (Gondi 2010) In addition, for the entire cohort there was no detriment in PFS (5.9 mos.) or OS (6.8 mos.) compared to historical controls.(Meyers 2004; Chang 2009) These data underscore the absence of survival impact of the rare relapse in the hippocampal avoidance region following HA-WBRT, the effectiveness of salvage radiosurgery, and the overall safety of HA-WBRT for patients with brain metastases.

We seek to build upon the results of RTOG 0614 and the highly promising findings,

safety profile and robust accrual of RTOG 0933 to develop a trial that more definitively addresses the hypothesis that hippocampal avoidance may decrease radiotherapy-induced memory decline. Thus, we propose a phase III study of WBRT and memantine versus HA-WBRT and memantine for patients with brain metastases, stratified by RPA class and prior treatment. The primary endpoint will be time to neurocognitive failure with **secondary endpoints such as quality of life, translational biomarkers, cumulative** incidence of intracranial relapse and overall survival.

2.2 Significance of the Study

As previously mentioned, 200,000 patients per year are treated with brain radiation for primary or metastatic brain tumors in the United States alone.(Robbins 2011) This is a very large patient population at risk of developing cognitive deterioration after radiotherapy, with a significant impact on patients, their caregivers, and society as a whole. Although our prior trial, RTOG 0614, showed better cognitive function over time with the addition of memantine, nearly 70% of patients still experienced cognitive deterioration by 6 months. Clearly, with this high rate of cognitive deterioration better treatments to prevent cognitive deterioration after radiotherapy are required. Therefore, in an effort to build on our earlier successes from RTOG 0614 and with the highly promising findings of RTOG 0933 we propose a randomized phase III trial of WBRT and memantine versus HA-WBRT and memantine for patients with brain metastases.

2.3 Neurocognitive Function Assessment

Neurocognitive outcomes have been recognized as being crucial in the brain metastasis population (Lin 2013). The Neurocognitive Clinical Trial Battery is a brief, sensitive, repeatable, highly standardized, objective battery of neurocognitive tests that have been demonstrated to be practical in terms of burden on the patient and site, with good compliance in multicenter clinical trials (Meyers 2004; Armstrong 2013; Brown 2013; Gilbert 2014). The following battery of tests was utilized in RTOG 0614, which serves as the basis for the current trial. Neurocognitive function will be assessed using the Hopkins Verbal Learning Test – Revised (HVLT-R, Benedict 1998), Trail Making Test (TMT, Tombaugh 2004), and the Controlled Oral Word Association (COWA, Ruff 1996). 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 8.3.1).

2.4 Patient-Reported Outcomes (PROs) and Health-Related Quality of Life (HRQOL)

Radiation therapy can affect brain functioning, resulting in alterations in neurologic and neurocognitive function. In addition, the treatment also can result in systemic effects that can result in symptoms such as fatigue that can impact function and cause alterations in health-related quality of life (HRQOL). Therefore, tumor response and impact on neurocognitive function may not fully describe the impact of this treatment on the patient. Patient-reported outcome measures (PROs) provide a mechanism to assess this benefit. (Gondi 2013) Evaluating the impact of this approach on both the acute effects of radiation therapy and the potential benefit of mitigation of neurocognitive decline is an important secondary endpoint of this study. We hypothesize that mean symptom severity

and mean symptom interference as well as mean neurologic and cognitive factor score and change score from baseline will be higher in the WBRT arm. We also predict that the total symptom severity on the M.D. Anderson Symptom Inventory Brain Tumor (MDASI-BT); the symptom interference subscale; and the specific items of fatigue, neurologic factor items and cognitive factor items score loss will be prognostic.

HRQOL will be measured using the EQ-5D-5L, a well established, validated measure that has been used in brain metastases populations.(Langley 2013; Takura 2010) 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) Both the EQ-5D-5L and MDASI-BT are brief and therefore are not a significant burden for patients to complete. Data will be analyzed longitudinally and compared between treatment arms.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA (24AUG2017)

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact IROC Philadelphia RT (see protocol cover page).

3.1 Patient Selection Guidelines (6/2/16)

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up. Patients must be willing to complete neurocognitive assessments at pre-specified time points outlined in the protocol.

3.1.2 Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception during the therapy (i.e. WBRT and memantine) part of the trial.

3.1.3 Submission of serum and whole blood is strongly encouraged for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. Samples will be submitted for banking for the translational research portion of this protocol and future studies. (See details in Sections 9 and 10.)

3.2 Eligibility Criteria (24AUG2017)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Prior to Step 1 Registration:

3.2.1 Brain metastases outside a 5-mm margin around either hippocampus must be visible on contrast-enhanced MRI performed ≤21 days prior to Step 1 registration. An allowed exception, regarding ability to image brain metastases, would be that patients who had undergone radiosurgery or surgical resection and are planning adjuvant WBRT do not have to have visible disease but do need a pre-surgery MRI or CT scan demonstrating brain metastases. However, the brain metastases could not have been within 5 mm of either hippocampus. (Only report on Step 1 if it meets the stratification variable; see the schema page.)

3.2.2 Patients **must** have a post gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan and an axial T2/FLAIR sequence. To yield acceptable image quality, the 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. This MRI must be obtained ≤21 days prior to step 1 registration. *See NRG-CC001 protocol page of the NRG website for imaging-specific frequently asked questions.*

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

3.2.3 Patients must provide study-specific informed consent prior to registration.

Prior to Step 2 Registration:

3.2.4 The following baseline neurocognitive assessments must be completed prior to Step 2 registration: HVLT-R, TMT, and COWA. The neurocognitive assessment will be uploaded into a folder in the NRG RAVE System for evaluation by Dr. Wefel. Once the upload is complete, within 1 business day a notification will be sent to the RA to proceed to Step 2.

NOTE: Completed baseline neurocognitive assessments can be uploaded at the time of Step 1 registration.

3.2.5 Pathologically (histologically or cytologically) proven diagnosis of solid tumor malignancy within 5 years prior to Step 2 registration. If the original histologic proof of malignancy is greater than 5 years, then pathological (i.e., more recent) confirmation is required (e.g., from a systemic metastasis or brain metastasis).

3.2.6 History and physical examination within 28 days prior to Step 2 registration

3.2.7 Age ≥ 18;

3.2.8 Karnofsky Performance Status of ≥70 within 28 days prior to Step 2 registration;

3.2.9 Adequate renal function ≤28 days prior to Step 2 registration defined as follows:

- Serum creatinine ≤ 3 mg/dL (265 μmol/L) and creatinine clearance ≥30 ml/min
- 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).

3.2.10 Patients may have had prior therapy for brain metastasis, including radiosurgery and surgical resection. Patients must have completed prior therapy by at least 14 days prior to Step 2 for surgical resection and 7 days for radiosurgery.

3.2.11 Negative serum pregnancy test (in women of childbearing potential) ≤14 days prior to Step 2. Women of childbearing potential and men who are sexually active must practice adequate contraception while on study.

3.2.12 Patients who are primary English or French speakers are eligible.

3.3 Ineligibility Criteria (24AUG2017)

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Prior external beam radiation therapy to the brain or whole brain radiation therapy.

- Prior single-fraction or fractionated radiosurgery is permitted.

3.3.2 Planned cytotoxic chemotherapy during the WBRT only; patients may have had prior chemotherapy.

3.3.3 Radiographic evidence of hydrocephalus or other architectural distortion of the ventricular system, including placement of external ventricular drain or ventriculoperitoneal shunt.

3.3.4 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 registration
- Chronic obstructive pulmonary disease exacerbation or other acute respiratory illness precluding study therapy at the time of registration
- 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 registration. Note also that HIV testing is not required for eligibility for this protocol.

3.3.5 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 involved in this study has unknown effects on the unborn fetus.

3.3.6 Prior allergic reaction to memantine

3.3.7 Current alcohol or drug abuse (may exacerbate lethargy/dizziness with memantine)

3.3.8 Intractable seizures while on adequate anticonvulsant therapy—more than 1 seizure per month for the past 2 months

3.3.9 Patients with definitive leptomeningeal metastases

3.3.10 Patients with brain metastases from primary germ cell tumors, small cell carcinoma, unknown primary, or lymphoma.

3.3.11 Contraindication to MR imaging such as implanted metal devices or foreign bodies

3.3.12 Contraindication to gadolinium contrast administration during MR imaging, such as

allergy or insufficient renal function

3.3.13 Current use of (other NMDA antagonists) amantadine, ketamine, or dextromethorphan

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (24AUG2017)

PRE-TREATMENT ASSESSMENTS	
Prior to *Step 1* Registration *(calendar days; may be required for eligibility)*	
Brain MRI w/ contrast*	21
Informed consent	Prior to registration
Prior to *Step 2* Registration*(calendar days)*	
(Required) Baseline neurocognitive: HVLT-R, TMT, COWA ***(upload required to proceed to Step 2)***	7
Histological/cytological evaluation	Within 5 yrs. prior to registration
Neurologic exam	28
History/physical exam	28
Karnofsky performance status	28
Serum creatinine, creatinine clearance, BUN	28
Serum pregnancy test *(if applicable)*	14
English or French is primary language *(English or French must be the patient's primary language)*	Pre-treatment
QOL: MDASI-BT, EQ-5D-5L	
(If patient consents) Specimen collection	
*Thin slice MRI required as outlined in Section 5.2.3.	

ASSESSMENTS DURING TREATMENT	
Assessments ***(All from the start of treatment)***	**From start of WBRT/HA-WBRT: at months 2, 4, and 6**
Physical exam	
Neurologic exam	
Karnofsky performance status	
Serum creatinine, creatinine clearance, BUN	
Brain MRI w/ contrast*	
(Required) Neurocognitive: HVLT-R, COWA, TMT (upload in RAVE required)	
QOL: MDASI-BT, EQ-5D-5L	
(If consent given) Specimen collection	
* Thin slice MRI is required for 6 month and highly recommended for 2 and 4 month follow-up as outlined in Section 5.2.3.	
All assessments are from the start of treatment	

ASSESSMENTS IN FOLLOW UP	
Assessments	**From start of WBRT/HA-WBRT: at month 12**
Physical exam	
Neurologic exam	
Karnofsky performance status	
Serum creatinine, creatinine clearance, BUN	
Brain MRI/CT w/ contrast	
(Required) Neurocognitive: HVLT-R, COWA, TMT (upload in RAVE required)	**2, 4, 6, and 12 months from the start of treatment**
QOL: MDASI-BT, EQ-5D-5L	
(If consent given) Specimen collection	

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Drug Therapy

Memantine should start the same day as WBRT/HA-WBRT and must start no later than before the fourth WBRT/HA-WBRT treatment.

If a patient is enrolled on the study and they are unable to acquire memantine they should remain on the study and otherwise proceed forward per study.

5.1.1 Both extended release memantine (Namenda XR) and twice daily memantine dosing will be allowed. 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 (10mg 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

Patients continue on memantine for 24 weeks.

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. Memantine is well absorbed after oral administration and absorption is not affected by food and therefore can be taken with or without food. Missed doses should be documented but patients should not try to make up missed doses. 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 (available on the forms page of the NRG-CC001 protocol page) 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.

5.2 Radiation Therapy (6/2/16)

Protocol treatment must begin within 21 calendar days after randomization.

NOTE 1: Patients can only be enrolled by treating physicians and institutions that have passed pre-enrollment benchmark cases for hippocampal contouring and HA-WBRT treatment planning. Treating physicians and institutions that were credentialed for NRG-CC003 (phase IIR/III study of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer) or RTOG 0933 (phase II study of hippocampal avoidance during WBRT for brain metastases) will be permitted to enroll patients on NRG-CC001, since benchmark cases are similar between these trials. However, the first case they enroll on NRG-CC001 will require pre-treatment review of hippocampal contouring and HA-WBRT treatment before proceeding with protocol treatment. See Section 8.4 for further details.

NOTE 2: The first patient enrolled from each credentialed treating physician and institution in Arm 2 (WBRT with hippocampal avoidance) will require a Pre-Treatment 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. See Section 8.4 for specifics on submission requirements.

NOTE 3: Treating physicians and institutions that passed one (1) pre-treatment review of a patient enrolled on the hippocampal avoidance arm of NRG-CC003 (phase IIR/III study of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer) will be permitted to enroll patients on NRG-CC001 without Pre-Treatment Review.

5.2.1 Treatment Technology

This protocol requires photon treatment. 3DCRT is allowed in Arm 1. Field-in-field approaches to 3DCRT to optimize homogeneity are permitted for Arm 1. Inverse planned IMRT is not allowed for Arm 1. IMRT is required for Arm 2. Fixed-gantry IMRT, helical tomotherapy or VMAT can be used for Arm 2. All participating sites must be credentialed for IMRT.

Megavoltage beam of 6MV or greater must be used for Arms 1 or 2, 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.

5.2.2 Immobilization and Simulation

Immobilization

Patients will be immobilized in the supine position using an immobilization device such as an Aquaplast mask over the head. Patients will be treated in the immobilization device.

Simulation Imaging

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. For patients

enrolled on Arm 2 (HA-WBRT experimental arm), 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.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-up
For Arms 1 and 2: Post *gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) axial MRI scan and axial T2 FLAIR sequence acquisitions.*
NOTE: ALTHOUGH NOT REQUIRED A PRECONTRAST AXIAL THREE-DIMENSIONAL IMAGING SEQUENCE IS ALSO STRONGLY ENCOURAGED.

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.

See NRG-CC001 protocol page of the NRG website for imaging-specific frequently asked questions.

These imaging sequences should be obtained with the patient in the supine position. The MRI sequences are **required at baseline** as an eligibility criterion for enrollment in the study and also **required at 6-month follow-up**. Immobilization devices used for CT simulation and daily radiation treatments need not be used when obtaining these imaging sequences, but an attempt should be made to image the patient in as close to the same plane as the CT simulation as possible to facilitate fusion of the MRI and CT images.

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 Imaging Co-Chairs for further information or assistance if needed.

Note: The MRI study is mandatory irrespective of randomization to the experimental or control arm of this study.

For Arm 2, the MRI for radiotherapy planning and treatment-planning CT should be fused semi-automatically for hippocampal contouring.

5.2.4 Definition of Target Volumes and Margins
For Arm 1, the target volume shall include the entire cranial contents, with flashing beyond skin and a minimum margin of 0.75 cm on the skull base as visualized on the digitally reconstructed radiograph (DRR) from the CT simulation scan. This flashing

accounts for beam penumbra and day-to-day set-up variation.

For Arm 2, 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 (see Section 5.2.5). No set-up margin is added.

5.2.5 Definition of Critical Structures and Margins

For Arm 1, care should be taken to minimize the dose to the lens. These can be contoured on the simulation CT and visualized on the DRR.

For Arm 2, 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.
OpticNerve_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.
OpticNerve_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.

5.2.6 Dose Prescription

For Arms 1 and 2, 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.

For Arm 1, dose is specified as the target dose, which shall be the dose on the central x-ray at mid-separation for two opposed coaxial equally weighted beams. "Compensating beams" that block hot spots (these hot spots are typically present along midline due to less tissue present in these regions compared to mid-brain) are allowed to achieve better dose homogeneity. All portals shall be treated during each treatment session.

For Arm 2, 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 (See Section 5.2.7).

5.2.7 Compliance Criteria

Arm 1: There are no compliance criteria specific to radiation therapy planning or delivery.

Arm 2: 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)	≤ 37.5	37.5 to 40	Dose to hottest 2% of PTV_3000
	$D_{98\%}$(Gy)	≥ 25	22.5 to 25	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)	≤ 9	9 to 10	Dose to 100% of Hippocampus
	D_{max}(Gy)	≤ 16	16 to 17	Dose to hottest 0.03 cc volume of Hippocampus
OpticNerve_L	D_{max}(Gy)	≤ 30	30 to 37.5	Dose to hottest 0.03 cc volume of OpticNerve_L
OpticNerve_R	D_{max}(Gy)	≤ 30	30 to 37.5 Gy	Dose to hottest 0.03 cc volume of OpticNerve_R
OpticChiasm	D_{max}(Gy)	≤ 30	30 to 37.5	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

5.2.8 Treatment Planning Procedures and Priorities

Arm 1: Three-dimensional approaches to radiotherapy planning will be used for patients enrolled in the WBRT reference arm. There are no treatment-planning priorities.

Arm 2: 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. OpticNerve_L or OpticNerve_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.

5.2.9 Dose Calculations

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.

Arm 2: 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.

5.2.10 Patient-specific QA

Arm 1: Patient-specific QA not required but should follow guidelines of enrolling institution.

Arm 2: 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.

5.2.11 Daily Treatment Localization/IGRT

Verification orthogonal films or images are required. For all forms of IMRT dose delivery, 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.

5.2.12 Case Review

Arm 1: No case review will be performed.

Arm 2: Case reviews will be ongoing and performed remotely for all patients enrolled in

Arm 2. Case reviews will be conducted by a team of Co-Chairs, including the Principal Investigators Drs. Brown and Gondi, and the Imaging Co-Chairs Drs. Bovi and Robinson.
Pre-treatment reviews are required. See section 5.2 for details

See Section 8.4 for specifics on submission requirements.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Permitted 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.

5.3.2 Prohibited Therapies

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 discouraged and other medications should be 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),
- 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

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.

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 protocol treatment.

* 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)]

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 protocol treatment

* 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)]

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agent

Commercial Agent

The commercial agent in NRG-CC001 is Memantine.

7.2 Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for adverse event (AE) reporting. The CTCAE version 4 is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP Adverse Event Reporting System (CTEP-AERS) application accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1389817585865).

7.2.1 Adverse Events (AEs)

Definition of an 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). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.2.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.3 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.3. **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events (IME) that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

7.2.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

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 following treatment with an agent under an NCI IND/IDE 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 reporting via CDUS unless otherwise specified.

7.3 CTEP-AERS Adverse Event Reporting Requirements (24AUG2017)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1389817585865.

Submitting a report via CTEP-AERS serves as notification to NRG Oncology 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. . Once internet connectivity is restored, an AE report must be submitted electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source documentation is requested by CTEP as the IND sponsor for this study and NRG as needed to complete adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and contact the NRG Operations Center (215-574-3191) for sourse document submission assistance.
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported

on the AE section of the appropriate case report form (see Section 13.2).

SAE Reporting Requirements During Course 1, Memantine + RT (weeks 1-3)
Expeditiously report all AEs that meet the requirements per the reporting table below during concurrent memantine and RT and for 30 days after end of RT.

SAE Reporting Requirements During Course 2, Memantine alone (weeks 4-24)
After the 30 day window from end of RT, only expeditiously report AEs *reasonably related* to protocol treatment that meet the requirements per the reporting table below; all other AEs (non-serious or unrelated) should be reported via routine AE reporting process.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Commercial Agent within 30 Days of the Last Administration of the Agent in this Study [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

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 commercially available 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:
- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercially Available Agent: None

8. REGISTRATION AND STUDY ENTRY PROCEDURES (26SEPT2017)

Access requirements for OPEN, Medidata Rave, and TRIAD: Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account.

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	

Documentation Required	IVR	NPIVR	AP	A
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

8.1 Site Registration Requirements (26Sept2017)

8.1.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be

processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org.

8.1.2 Requirements for NRG-CC001 Site Registration (26Sept2017)

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- IROC Credentialing Status Inquiry (CSI) Form
  NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component.
- Credentialing documentation received from IROC Houston for this trial- See Section 8.4 Table for details.
- IRB/REB approved consent (Non-North American and Canadian sites only: English and native language versions*) ***Note**: International and Canadian Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology (described below).
- Other RT-Specific Requirements: See Section 8.4.
- Neurocognitive Function Testing Certification: See Section 8.3.1.

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab→ Regulatory Submission

When applicable original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:
Check the status of your site's registration on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

French Speaking Canadian and International Institutions:
Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB 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. Sites are NOT permitted to translate the Neurocognitive Tests. For sites testing native French speakers, the French versions of the tests must be obtained from the NRG Oncology website just as the English versions are obtained from the NRG Oncology website.

8.2.3 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

Prior to clinical trial commencement, Canadian institutions must also complete and submit via the Regulatory Submission portal on the CTSU website:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form.

8.3 Pre-registration Requirements

8.3.1 Neurocognitive Function Testing Certification

Only a certified test administrator is permitted to administer the neurocognitive tests to study participants. Test administrators must meet certification requirements for administering neurocognitive assessments (see Appendix II and the Neurocognitive Training Procedure Letter on the NRG Oncology website). Upon review and successful completion of the Neurocognitive Certification process, Jeffrey S. Wefel, PhD, Neurocognitive Co-Chair, will notify both the certified examiner and NRG Oncology that the examiner has successfully completed this requirement. The certified test administrator must be proficient in the language (English or French) in which the test is administered to the patient. Refer to the protocol-specific material on the NRG Oncology website for

certification requirements.

8.4 RT-Specific Pre-Registration Requirements (26Sept2017)

All sites must be IMRT Credentialed. For detailed information on the specific technology credentialing requirements 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, the IROC-Houston QA Center will notify your institution and NRG Headquarters when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. This document must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

Benchmark Testing

In order for a site to receive official credentialing for HA-WBRT, the institution and the treating physician must have passed benchmark testing for hippocampal contouring and HA-WBRT treatment planning AND pass the pre-treatment review on one case enrolled on NRG-CC001. Please note the exceptions to this requirement below in Notes 2, 3, and 4. **Benchmark testing is limited to two (2) physicians per site. Benchmark testing for hippocampal contouring and HA-WBRT treatment planning is no longer available.**

A treating physician who has not participated in or passed benchmark testing can enroll and treat patients on study so long as the patient's contouring and HA-PCI treatment plan is reviewed by another physician who has passed benchmark testing at the treating site.

Treating physicians and institutions credentialed for RTOG 0933 (Phase II study of hippocampal avoidance during WBRT for brain metastases) or NRG-CC003 (Phase IIR/III of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer) can enroll patients in this trial without having to repeat the Benchmark QA test. However, the first case they enroll on NRG-CC001 will require pre-treatment review of hippocampal contouring and HA-WBRT treatment before proceeding with protocol treatment.

While the trials limit credentialing to 2 physicians per site, the trials do NOT limit accrual to 2 physicians per site. Instead, we ask sites to enable any physician to accrue a patient to this study and to develop the hippocampal contours and hippocampal avoidance IMRT plan (should the patient be randomized to the experimental arm). However, we mandate that if a patient is enrolled by a non-credentialed physician, they ask one of the credentialed physicians at their site to review the contours/plan to ensure that they meet protocol criteria. When enrolling the patient, the system asks two questions: 1) Who is the enrolling the physician? and 2) Who is the credentialed physician who will be approving the contours? Again, these do not need to be the same physician.

To be Grandfathered from 0933 or CC003, complete a Credentialing Status Inquiry (CSI) Form (see the procedures and instructions table below) must be submitted in order to receive a letter and have RSS updated.

If an institution has successfully passed the Benchmark test for HA-WBRT planning on a non-VMAT (Volumetric Modulated Arc Therapy) IMRT modality, but would like to treat patients using VMAT, then the site will need to repeat the Benchmark test for HA-WBRT planning for the VMAT platform. In this case, the site can use their previous Benchmark submission.

RT Credentialing Requirements	NRG-CC001		
	Treatment Modality		Key Information
	3DCRT (Arm 1)	IMRT Mandatory for all sites (Arm 2)	
Facility Questionnaire		✓	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.
Credentialing Status Inquiry Form		✓	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Benchmark Cases		✓	Benchmark cases are to be downloaded and completed by each treating physician at each institution before submission to IROC-Philadelphia RT via TRIAD. Sites are to generate an IMRT plan for WBRT with hippocampal avoidance as per protocol criteria. See below for further details. EXCEPTION: Treating physicians and sites credentialed for RTOG 0933 (phase II study of hippocampal avoidance during WBRT for brain metastases) or NRG-CC003 (phase IIR/III study of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer) will not be required to pass Benchmark Testing for NRG-CC001.
Phantom Irradiation		✓	An anthropomorphic phantom study provided by the IROC-Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC -Houston web site (http://irochouston.mdanderson.org).
Additional Information			
Credentialing Issued to:			
Institution		✓ ✓	Credentialing requires passing of benchmark testing AND passing of pre-treatment review of one (1) case enrolled on NRG-CC001. Credentialing for HA-WBRT treatment planning is site-specific. Credentialing for hippocampal contouring will be specific to each treating physician. IROC-Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.
Radiation Oncologist		✓ ✓	

8.4.1 Digital RT Data Submission to NRG Oncology Using TRIAD

TRIAD is the image exchange application used by the NRG Oncology. TRIAD provides sites participating in NRG clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account, and be registered as an AP, NPIVR or IVR. Please refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- To submit images, the site physics user must be on the site's affiliated rosters and be assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found at http://www.rtog.org/CoreLab/TRIAD.aspx.

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

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

8.5 Patient Enrollment (26Sept2017)

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.

8.5.1 Oncology Patient Enrollment Network (OPEN)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org

or from the OPEN tab on the CTSU members' web site https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN site staff should verify the following:

- The following baseline neurocognitive assessments must be completed prior to Step 2 registration: HVLT-R, TMT, and COWA (see Section 3 for details).
- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and 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.

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

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: websupport@acr.org or call the NRG Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

9.0 DRUG INFORMATION

9.1 Investigational Study Agent

Not applicable for this study.

9.2 Commercial Agent: Memantine

Use of twice daily or extended release dosing is allowed. See Section 6.

Adverse Events

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.2.1 Availability/Supply

Please see Section 6 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 Memantine in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption. The IND exemption letter is available on the NRG Oncology website via the regulatory resources tab of the NRG-CC001 page.

10. PATHOLOGY/BIOSPECIMEN

10.1 Biomarkers (6/2/16)

For patients undergoing brain irradiation, there are no biomarkers to predict which individuals will experience substantial cognitive impairment. Data on this topic is speculative in nature, and primarily extrapolated from our rapidly growing knowledge of the mechanism of Alzheimer's type dementia, which resembles radiation induced dementia (Raber 2010). Contributing factors likely include inflammation and neuroimmune-mediated toxicity, alterations in growth factor signaling and parenchymal/neural stem cell as well as direct neuronal damage, endothelial cell damage and vascular dysfunction, oxidative damage and genetic susceptibility. In order to be prepared to correlate biomarkers to the development of neurocognitive decline after brain irradiation, serum will be collected during this trial at baseline (after registration, but prior to treatment), at 2, 4, 6 and 12 months from the start of radiation. Whole blood also will be collected at baseline. Possible analyses of these body fluid biospecimens are described below. The specimens and assays to be collected are consistent with that obtained by predecessor trials including RTOG 0614, NCCTG 103 (an RTOG endorsed study), and to a lesser extent, RTOG 0933. This will allow for longitudinal study comparisons and validation of candidate biomarkers.

10.1.1 Genetic Markers

The apolipoprotein E (ApoE) gene encodes for ApoE and is located on chromosome 19. ApoE is involved in the uptake, transport and distribution of lipid, is expressed at high levels in the brain, and is believed to play an important role in neuronal repair and synaptic function (Mahley 2009, Chen 2010). ApoE is polymorphic and has three major alleles, ApoE2, ApoE3, ApoE4. The E4 allele has been associated with cognitive dysfunction after damaging events such as cardiac bypass surgery (Tardiff 1997) and traumatic brain injury (Nicoll 1995, Jordan 1995). Additionally, testing of middle-aged E4 carriers reveals cognitive difficulties (Greenwood 2009). Finally, the E4 allele is an established risk factor for Alzheimer's dementia (Caselli 2009). Data suggest that patients having the Apo E4 isoform realize Alzheimer's dementia far earlier than those without it[12]. This allele is present in 16% of the general population and 50% of patients with late onset Alzheimer's dementia (Teunissen 2002). Given potentially similar mechanisms of dementia between Alzheimer's and radiation-induced dementia (e.g. vascular or metabolic), Apo E4 genotyping may prove to be a predictor of radiation induced neuronal damage. Apo E genotyping will be performed to assess whether a subgroup of patients exists that is genetically predisposed to developing neurocognitive decline (or neuroprotection). As this field continues to evolve, it is expected that genome wide association studies will also be important in identifying other possible biomarkers and accordingly, adequate whole blood will be obtained to allow for these future explorations.

- *Inflammatory Markers*
  Markers of inflammation are elevated with aging and their increase has been associated with neurocognitive decline (Krabbe 2004, Yaffe 2003). Epidemiological and retrospective data reveals an improvement in neurocognitive function with the use of NSAID's in patients with Alzheimer's dementia, hence, supporting an inflammatory process involved in neurocognitive decline (Teunissen 2002). Chronic inflammation as a result of mass effect from tumor or treatment (radiation) related inflammation may be associated with neurocognitive deficits and can be measured in

plasma. Interleukin 1 (IL-1), Interleukin 6 (IL-6), and Tumor Necrosis Factor alpha are proinflammatory cytokines that are a measure of inflammation and have been shown to be elevated in patients with Alzheimer's dementia (Blum-Degen 1995, Martinez 2000, Cacabelos 1994, Tarkowski 1999). In this study, inflammatory biomarkers, serum will be obtained at baseline (after registration, but prior to treatment) and at the various time points indicated above in order to assess whether inflammation changed as a result of type of therapy and what impact or correlation this has with cognitive outcomes.

10.1.2 Oxidative Stress

Evidence suggests surrogates for oxidative damage may be biomarkers for radiation-induced neurotoxicity (Abayomi 1996; Roman 1995). Decreased cerebral perfusion results in decreased oxygen and glucose delivery that eventually leads to energy deprivation which is the cause of oxidative stress in the brain (Lancelot 1998). Oxidative stress from either tumor or radiation may be a predictor and measure of neurocognitive decline. Isoprostanes are one of the best-described indicators of oxidative stress and can be measured *in vivo* (Gondi 2010). Our approach to measuring oxidative stress will consist of quantifying protein carbonyl content spectrophotometrically, measuring lipid hydroperoxides, and finally, quantitating isoprostane levels in patient serum.

10.1.3 Hormone and Growth Factors

Aging and memory decline is associated with the disruption of hormone regulation, including glucocorticoids, gonadal steroids, and growth hormone (Gondi 2013). Cortisol, human chorionic gonadotropin (hCG), insulin-like growth factor-1 (IGF-1), and neuronal growth factor (NGF), have all recently been associated with cognitive decline in Alzheimer's disease (Ding 2006, Tuszynski 2005). ELISA testing of serum specimens for each hormone and growth factor will be performed following completion of the trial.

10.2 Biospecimen Submission Table (24AUG2017)

10.2.1 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.

See detailed specimen collection/processing/shipping instructions on the protocol-specific page on the NRG Oncology website.

Optional Study: Correlation of biomarkers to the development of neurocognitive decline after brain irradiation

The specimens are being collected in order to be prepared to correlate biomarkers to the development of neurocognitive decline after brain irradiation (see Section 10.1 for further details).

- Required Form: ST form (include study #, case #, patient initials, NRG/NCI institution ID# and name, treatment time point of specimens)
- Biospecimen Kits: Available from the NRG Oncology Biospecimen Bank-San Francisco
- Shipping days for frozen biospecimens: Monday-Wednesday (U.S. sites); Monday-Tuesday

(Canada and Non-North American).

- Shipping costs: One return label per case is provided for batch shipping of frozen biospecimens only.

For questions, contact:
NRG Oncology Biospecimen Bank-San Francisco
415-476-7864/FAX 415-476-5271
NRGBB@ucsf.edu

Specimen Type	Collection Time Points	Collection Information and Requirements/Instructions for Site	Shipping *For detailed specimen collection and shipment instructions, see protocol-specific website*
Specimen 1: Serum-red top tube (Collection tube is not included in kit- is provided by site)	Baseline: Prior to WBRT or HA-WBRT 2, 4, 6 and 12 mos. following the start of WBRT or HA-WBRT	Processed Serum aliquots – minimum of 0.5 mL per aliquot in five (5) 1 mL cryovials. Store at -80°C (-70°C to -90°C) until ready to batch ship on Dry ice. Storage: -80°C and ship frozen	Serum sent frozen in batches on dry ice via overnight courier to NRG Biospecimen Bank - San Francisco
Specimen 2: Whole Blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube (purple/lavender top) and mix (Collection tube is not included in kit- is provided by site)	Baseline: Prior to WBRT or HA-WBRT	Frozen whole blood samples containing 1.0 mL per aliquot in three (3) 2 mL cryovials Store at -80°C (-70°C to -90°C) until ready to batch ship on Dry ice.	Whole blood sent frozen on dry ice with serum samples by overnight courier to NRG Biospecimen Bank - San Francisco

11. SPECIAL STUDIES (NON TISSUE)

11.1 Imaging Biomarkers (6/2/16)

Although cognitive decline is a known potential complication following WBRT it is not well understood why some patients decline while others do not or why some patients decline more than others. Previous research has shown a relationship between treatment specific variables and the degree of brain injury following radiation therapy. Higher total radiation dose, higher dose per fraction, and increased brain volume irradiated have all been associated with greater radiation-induced brain injury (Roman, 1995). However, holding dose constant, the role of patient specific variables in influencing outcome following radiation has not been well investigated. A few studies have shown a relationship between age at time of treatment and neurological injury following radiation. Older age at time of treatment has been associated with poorer neurological outcome and a greater degree of treatment related white matter damage (Conill 2007; Swennen 2004;

Wassenberg 2001). The presence of cardiovascular risk factors, such as hypertension and history of smoking, has also been associated with increased white matter damage following WBRT in some (Swennen 2004) but not all studies (Conill 2007). There is data suggesting that the greater amount of white matter lesion burden prior to WBRT is associated with increased white matter damage following treatment (Conill 2007; Wassenberg 2001). However, these studies were limited by relatively small sample sizes, utilization of qualitative rather than quantitative methods for measuring white matter injury, and lack of control for the effects of the disease (e.g., white matter changes from lesion induced edema) and other treatments (e.g., radiosurgery) on white matter findings. Sabsevitz, Bovi, et al (2013) published the first study to use quantitative volumetric methods in a relatively large group of brain metastases patients to examine the effects of pre-treatment white matter status on treatment induced white matter injury. Pre-treatment white matter health was shown to be a stronger predictor of post treatment white matter damage than age when radiated, dosing parameters, and cardiovascular risk factors.

A body of data also exist exploring additional variables predictive of neurocognitive decline in the spectrum from healthy aging to mild cognitive impairment (MCI) and subsequent Alzheimer's disease (AD). In addition to genetic (ApoE4) and baseline clinical variables (female sex, family history, and education, etc.), hippocampal volumetry with MRI has emerged as another possible imaging biomarker predictive of cognitive decline. (Teipel 2013) A high-resolution structural MRI only requires 5-10 minutes of time, and standardized manual and automated hippocampus volumetry analysis methods are well described. (Jack 2008) Manual volumetry has been shown to have 80-90% diagnostic accuracy in distinguishing AD vs. controls (Jack 1997) and modern automated volumetry has a high correlation with the more labor intensive manual techniques ($R2 > 0.8$) while retaining similarly strong group discrimination. (Csernansky 2005, Colliot 2008) A number of studies also have demonstrated that baseline hippocampal volume, either alone or in concert with other clinical and biologic variables, is a significant predictor for subsequent cognitive decline. In one large study of 1,156 cognitively normal patients who participated in the Mayo Clinic Study of Aging MRI/MRS study from 2005-2010, at a median follow-up of 2.8 years, 214 patients had progressed to MCI or dementia (6.1%/yr, 95% CI 5.3-7.0%). (Kantarci 2013) Likewise, baseline hippocampal volume also may predict for rate of neurocognitive decline. In a study of 211 participants of the Rush Memory and Aging Project, faster cognitive decline was associated with smaller hippocampal volumes at baseline. (Fleischman 2013)

Highly promising preliminary data from RTOG 0933 has demonstrated that WBRT with hippocampal avoidance (HA-WBRT) significantly reduces the risk of neurocognitive decline compared with historical controls, as measured by the primary endpoint, mean relative loss in HVLT-R delayed recall at 4 months (7% vs 30%, $p=0.0003$). (Gondi 2013) These results provide additional compelling evidence to a growing body of clinical literature supporting the hippocampus and/or the white matter tracts leading into and out of the hippocampus as a centerpiece for modulation of neurotoxicity after cranial radiotherapy. (Gondi 2013, Peiffer 2013) Notably, of the 42 analyzable patients at 4 months, 14 (33.3%) had significant deterioration on HVLT-R delayed recall (as assessed using the reliable change index) compared with pre-treatment testing. (Gondi 2014) A

preliminary analysis of clinical variables revealed that only baseline neurologic function (defined as at least some symptoms versus no symptoms) was predictive of decline in HVLT-R immediate recall and delayed recall on multivariate analysis. Similarly, in a combined analysis of neurocognitive and quality of life data from two large prospective trials evaluating the impact of PCI on SCLC (RTOG 0212) and NSCLC (RTOG 0214), only baseline impairment in HVLT-R and age > 60 were predictive of subsequent decline in HVLT-R on multivariate analysis. (Gondi 2013)

We hypothesize that (1) abnormal FLAIR volume and/or hippocampal volume at baseline will be predictive of subsequent neurocognitive decline after WBRT or HA-WBRT, (2) baseline imaging biomarkers will identify patients who derive the least benefit from HA-WBRT, and (3) changes between baseline and 6 month imaging will correlate with neurocognitive decline.

For data consistency, it is very important that a standardized protocol be obtained. A 3 Tesla MRI is preferred (minimum 1.5 Tesla MRI system is required). If possible participants should be scanned on the same MRI scanner at each visit. MRI protocols meeting the study requirements are available for download from ADNI (*http://adni.loni.usc.edu/methods/documents/mri-protocols*). Assistance with site-specific scanner configuration or imaging workflows may be obtained by contacting the Modality Co-Chair/Radiology, Tammie L.S. Benzinger, MD, PhD, benzingert@wustl.edu.

MRI FLAIR DICOM images will be downloaded to a local workstation for processing. Abnormal FLAIR volumes will be created in a semi-automated fashion by empirically thresholding the FLAIR images to highlight regions of abnormality, followed by manual editing to exclude normal regions misclassified (e.g., gray matter, choroid plexus, etc.). Volumes will be edited by three trained individuals using a consensus approach who are blind to the neurocognitive outcome data. FLAIR volumes will be measured throughout the brain, excluding cerebellum and midbrain structures. In order to address the potential confounding effects of the disease on white matter findings, semi-automated methods will be used to highlight metastases and any surrounding (i.e., contiguous voxels) abnormal FLAIR and the latter volumes will be subsequently masked out or removed from analyses.

Hippocampal volumes (R, L, bilateral) will be extracted. The physician contoured hippocampal volumes will be calculated from the RT STRUCT data set. If only the composite bilateral HIPPOCAMPUS volume is available from the RT STRUCT data set, it will be separated manually into HIPPOCAMPUS_L and HIPPOCAMPUS_R for purposes of analysis. Automatically derived hippocampal volumes also will be calculated with FreeSurfer software (Martinos Center for Biomedical Imaging) using the original 3D MRI DICOM files per a validated process established through the Alzheimer's Disease Neuroimaging Initiative (ADNI). Hippocampal volumes (including ratios of HIPPOCAMPUS to CTV and PTV) will then be correlated with declines in neurocognitive outcomes. Hippocampal volumes as derived from physician contours and auto-contours will be analyzed to determine which, if any, have the highest predictive value.

11.1.1 Study eligibility requires a gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan along with axial T2/FLAIR sequence acquisitions. A pre-contrast SPGR, MP-RAGE, or TFE scan is also highly recommended. Imaging is to be obtained within **21 days** of Step 1 registration. The purpose of this baseline imaging study is to rule out intracranial metastases prior to enrollment and for hippocampal contouring should the patient be randomized to the hippocampal avoidance experimental arm of this study. This imaging study will be submitted for centralized quality assurance review of hippocampal contouring and hippocampal avoidance treatment planning.

For this exploratory analysis of imaging biomarkers, the MRI scan also will be used to provide assessment of white matter changes and hippocampal volumetry. It is required that MRI imaging be submitted at baseline and 6 months post treatment to compare the imaging biomarkers in patients treated on the standard and experimental arms. As exploratory objectives of this study, T2/FLAIR and SPGR, MP-RAGE or TFE sequences will be submitted for central analysis. Abnormal FLAIR volumes will be created in a semi-automated fashion by trained individuals using a consensus approach and blinded to the cognitive outcome data. Automated hippocampal volumetry will be performed on the pre-contrast SPGR, MP-RAGE or TFE sequences using FreeSurfer (Boston, MA). FreeSurfer has been widely used in multiple large multi-institutional trials and, for hippocampal volumetry in particular, has been shown to be highly accurate compared with expert manual tracing (Morey 2009).

- *Post gadolinium contrast-enhanced three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MP-RAGE), or turbo field echo (TFE) MRI scan and axial T2 FLAIR sequence acquisitions.* ***NOTE: ALTHOUGH NOT REQUIRED A PRECONTRAST AXIAL THREE-DIMENSIONAL IMAGING SEQUENCE IS ALSO STRONGLY ENCOURAGED***

- To yield acceptable image quality, the pre (if performed) and post gadolinium contrast-enhanced three-dimensional SPGR, MP-RAGE, or TFE MRI scan should use the smallest possible axial slice thickness not exceeding 1.5 mm.

- See NRG-CC001 protocol page of the NRG website for imaging- specific frequently asked questions.

- If your institution doesn't 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 may contact the Imaging Co-Chairs for further information or assistance if needed. MRI scans are non-invasive and provide no additional risk to the patient.

Submission of imaging will be required on all patients. See Section 8.4 for specifics on submission requirements and procedures. All imaging will be anonymized by TRIAD to ensure patient confidentiality.

11.2 Neurocognitive Evaluation

The Neurocognitive Clinical Trial Battery is a brief, sensitive, repeatable, highly standardized, objective battery of neurocognitive tests has been demonstrated to be practical in terms of burden on the patient and site, with good compliance in multicenter clinical trials (Meyers 2004; Armstrong 2013; Brown 2013; Gilbert 2014). The tests have published normative data that take into account age and, where appropriate, education and gender. As in RTOG 0614, six alternate forms of the HVLT-R and two alternate forms of the COWA will be employed to minimize practice effects.

11.3 Patient Reported Outcomes (all patients are required to participate)

Symptom Burden (NOTE: Translations not available for this protocol; enrollment restricted to English and French-speaking participants.)

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, Mendoza et al. 2006, Armstrong, Vera-Bolanos et al. 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 also are measured on 0-10 scales.

Health Related Quality of Life

Health related quality of life will be assessed using the EQ-5D-5L. 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 & Janssen, 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.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews (6/2/16)

For Arm 2 Only: The Radiation Oncology Co-Chairs, Paul Brown MD, Vinai Gondi MD, Joseph Bovi MD, Cliff Robinson MD, Deepak Khuntia MD, David Grosshans MD, PhD, or Andre Konski MD will perform an RT Quality Assurance Review after IROC-Philadelphia RT has received complete data. These reviews will be completed remotely and will be ongoing. 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 for all cases enrolled, whichever occurs first. The scoring mechanism is: **Per Protocol, Acceptable Variation, and Unacceptable Deviation**.

12.2 Drug Quality Assurance Reviews

The Co-Principal Investigator, Paul Brown, MD, will perform a Quality Assurance Review of all patients on this trial. The goal of the review is to evaluate memantine protocol compliance. The review process is contingent on timely submission of treatment information data as specified in Section 13.2. The scoring mechanism is: **Per Protocol/Acceptable Variation, Unacceptable Deviation, and Not Evaluable**.

Dr. Brown will perform a Quality Assurance Review after NRG Headquarters has received complete data for the first 20 cases enrolled. Dr. Brown will perform the next review after NRG Headquarters has received complete data for the next 20 cases enrolled. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

13.1 Data Management/Collection (26Sept2017)

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). To access iMedidata/Rave, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Each person responsible for data entry must be on the NRG roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata

(iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Once an account is activated, eLearning modules will be available for Rave RDC instructions. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts also will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2 Summary of Data Submission

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 Sections 7.1 and 7.2 for information about expedited and routine reporting.

Summary of Data Submission: Refer to the NRG Oncology website.

See Section 8.4 for TRIAD account access and installation instructions.

All neurocognitive materials for every patient at every time point must be uploaded to Medidata Rave® within 7 days after test administration.

See Section 8.4 for TRIAD account access and installation instructions.

13.3 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design (24AUG2017)

14.1.1 Stratification

Patients will be stratified according to RPA class (I vs. II) and prior therapy (none vs. radiosurgery or surgical resection).

14.1.2 Randomization

Patients will be randomized 1:1 to receive WBRT 30 Gy/10 fractions plus memantine or WBRT with Hippocampal Avoidance using IMRT 30 Gy/10 fractions plus memantine

using a permuted block procedure (Zelen 1974).

14.1.3 Total Accrual

The total accrual for this study will be 510 patients as described in detail in Section 14.3.3.

14.2 Study Endpoints

14.2.1 Primary Endpoint

Time to neurocognitive failure, as measured by neurocognitive decline on HVLT-R, COWA, and TMT Parts A and B

14.2.2 Secondary Endpoints

- Preservation of neurocognitive function, as measured by neurocognitive decline on HVLT-R, COWA, and TMT Parts A and B, and Clinical Trial Battery Composite (CTB COMP) score
- Symptom burden, as measured by the MDASI-BT
- Health outcomes, as measured by the EQ-5D-5L
- Intracranial progression

14.2.3 Exploratory Endpoints

- Effect of white matter injury and hippocampal volume on neurocognitive function
- Effect of RTOG RPA and the diagnosis-specific graded prognostic assessment (DS-GPA) on neurocognitive function
- Correlation of symptom burden and anxiety/depression with neurocognitive function
- Relationship between EQ-5D-5L and MDASI-BT mood variables and neurocognitive function.

14.3 Primary Objectives Study Design (24AUG2017)

14.3.1 Primary Hypothesis and Endpoints

The primary hypothesis of this phase III study is that the addition of HA-WBRT as compared to WBRT will increase time to neurocognitive failure, as measured by cognitive decline on a battery of tests (HVLT-R, COWA, and TMT), from 53.8% in the WBRT arm to 42.8% in the HA-WBRT arm at 6 months.

14.3.2 Definitions of Primary Endpoints and How These Will Be Analyzed

Neurocognitive failure is the first failure, defined as a neurocognitive decline using the reliable change index (RCI) on at least one of the following assessments: HVLT-R, TMT, or COWA (Jacobson 1991; Chelune 1993). The HVLT-R has 3 parts that will be analyzed separately for decline: Total Recall, Delayed Recall, and Delayed Recognition. The TMT has 2 parts that will be analyzed separately: Part A and Part B. This endpoint will be evaluated at the time points when neurocognitive testing is administered. In RTOG 0614, this endpoint showed a statistically significant difference in favor of the arm receiving WBRT and memantine compared to the arm receiving WBRT and placebo (Brown 2012). Of note, composite neurocognitive endpoints such as this have been used in many other studies such as the landmark trial by Meyers et al. evaluating cognitive function before and after WBRT for patients with brain metastases (Meyers JCO 2004). Because of these results and the fact that this composite endpoint encompasses multiple cognitive domains, it is being used as the primary endpoint in this study.

The cumulative incidence approach will be used to estimate the median time to

neurocognitive failure to account for the competing risk of death. Gray's test will be used to test for statistically significant difference in the distribution of neurocognitive failure times (Gray 1988). The cause-specific Cox proportional hazards regression model will be used to evaluate the effect of stratification variables (RPA class and prior therapy) and other baseline characteristics, such as KPS, DS-GPA grade, FLAIR volume change, and hippocampal volume, on time to neurocognitive decline (Cox 1972).

Analysis for Reporting the Initial Treatment Results

This major analysis will occur after at least 233 NCF failure events have been observed. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rate of treatment delivery
- observed results with respect to the primary and secondary endpoints

The analysis will be conducted on an intent-to-treat basis using all randomized at-risk patients. Patients will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit will be tested using Gray's test with a 2-sided significance level of 0.05. Additional analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factors included as fixed covariates, as well as any factors that show an imbalance between the arms (e.g. age, gender, race, etc.) or mentioned in the analysis plan. Where feasible, treatment comparisons with respect to the primary endpoint (NCF) will be compared within each ethnic and racial category.

14.3.3 Sample Size and Power Calculations

In this phase III study, the primary endpoint is time to neurocognitive function failure and the potential impact of HA-WBRT compared to WBRT. Due to the competing risk of death, the method described by Pintilie (2002) will be used to estimate sample size using data from RTOG 0614. This study showed a significant 11% reduction in neurocognitive function failure compared to patients receiving placebo (p=0.01) using the cumulative incidence method and Gray's test. The memantine arm showed a neurocognitive function failure of 53.8% at 6 months (corresponding to a monthly hazard of 0.198 utilizing Pintilie's method) and a death rate (as a competing risk) of 30.7% (corresponding to a monthly hazard of 0.113). It is assumed there is an 11% absolute reduction in neurocognitive function failure (monthly hazard rate of 0.129) and a similar death rate using HA-WBRT, resulting in a hazard ratio of 0.65. Assuming two-sided α=0.05, 230 events in both arms combined are required to achieve 90% statistical power utilizing Pintilie's method. In order to estimate the sample size, the probability of neurocognitive function failure provided that some failures may not be observed due to death, needs to be calculated. The following formula will be used:

$$P_{ev} = \frac{\lambda_{ev}}{\lambda_{ev} + \lambda_{cr}} * \left(1 - \frac{e^{-(\lambda_{ev}+\lambda_{cr})*f} - e^{-(\lambda_{ev}+\lambda_{cr})*(f+a)}}{(\lambda_{ev} + \lambda_{cr}) * a}\right)$$

where *ev* represents the event of interest, *cr* represents the competing risk, *a* is the length of the accrual period and *f* is the additional follow-up time after accrual ends. Using this formula, the probability of neurocognitive function failure over a 63 month study (57 months for accrual and 6 months of additional follow-up) for WBRT is 0.631 and for HA-WBRT is 0.570. The overall probability of neurocognitive function failure for the duration of the study is 0.601. The total sample size required is the number of events required divided by the probability of neurocognitive function failure, resulting in 382 patients. Due to possible ineligible and non-compliant patients, the sample size will be increased by 25%. Thus, **510 patients will need to be accrued** in order to ensure 382 evaluable patients.

14.4 Study Monitoring of Primary Objectives (6/2/16)

Interim Analysis for the Data Monitoring Committee

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pre-treatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoints, time to neurocognitive failure, or any secondary endpoints, with the exception of reporting of adverse events.

14.5 Accrual Considerations (24AUG2017)

14.5.1 Accrual Rate

For the preceding trial, RTOG 0614, the expected accrual rate was 12 patients per month over 4 years. In actuality, the trial accrued at a rate of 20 patients per month and completed accrual in just over 2 years, 2 years sooner than anticipated. RTOG 0933 accrued 113 patients at an accrual rate of 6 patients per month. Target accrual was reached 19 months from trial activation, significantly sooner than the initially projected total accrual period of 26 months. Therefore, for the current proposed trial, we would expect a uniform accrual rate of 9 patients per month. Accrual will be monitored with respect to DCP accrual guidelines.

14.5.2 Accrual Goal

The accrual goal is 510 patients.

14.5.3 Study Duration

Based on patient accrual in previous RTOG brain metastases studies, there will be negligible accrual during the initial 6 months while institutions are obtaining IRB

approval. From activation, the study would complete accrual in 63 months with 57 months of active accrual.

14.5.4 Estimated Duration for Completion of Primary Endpoint

The design accounted for 6 months of additional follow-up after meeting the target accrual which would result in completion of the primary endpoint approximately 69 months from group activation or 63 months from study activation.

14.6 Secondary or Exploratory Elements (including correlative science aims) (24AUG2017)

14.6.1 Secondary Hypotheses and Endpoints

- Evaluate neurocognitive function, as measured by the HVLT-R, COWA, TMT and CTB COMP (the arithmetic mean of the HVLT-R, TMT, and COWA outcomes). Specifically, it is hypothesized neurocognitive function will be preserved in the HA-WBRT compared to the WBRT arm.
- Evaluate symptom burden as measured by the M.D. Anderson Symptom Inventory-Brain Module (MDASI-BT). Specifically, it is hypothesized that the following subscales on the MDASI-BT will result in higher symptom burden for patients receiving WBRT as compared to HA-WBRT: symptom severity, symptom interference, neurologic factor, and neurocognitive factor score. It is also hypothesized that baseline symptom severity and symptom interference along with the specific items of fatigue, neurologic factor items, and neurocognitive factor items will be prognostic of neurocognitive decline.
- Assess quality adjusted survival using the EQ-5D-5L.
- Evaluate overall survival
- Evaluate intracranial disease progression
- Evaluate adverse events as measured by CTCAE v4.0

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Neurocognitive Function

Neurocognitive function will be measured by the HVLT-R, COWA, and TMT. The HVLT-R has 3 parts that will be analyzed separately: Total Recall, Delayed Recall, and Delayed Recognition. The TMT also has 2 parts that will be analyzed separately: TMT Part A and TMT Part B. The COWA has a single outcome measure that will be analyzed. Standardized scores that adjust for age, education, and gender when necessary will be analyzed. For discrete time point analyses, the change from baseline to each follow-up time point (2, 4, 6, and 12 months from the start of treatment) will be calculated and compared between treatment arms using a t-test or Wilcoxon-Mann-Whitney test, depending on the normality of the data. Neurocognitive decline using the reliable change index (RCI) for the HVLT-R, COWA, and TMT also will be compared between treatment arms at each follow-up time point using Fisher's exact test (Jacobson 1991; Chelune 1993).

A mixed effects model will be used to assess changes of standardized neurocognitive scores across time using all available data while adjusting for stratification variables and other baseline characteristics. Mixed models are a general class of models for analyzing repeated measures data, which allow modeling of the covariance among the repeated measures as well as random effects such as patient-specific intercepts and slopes and can

incorporate fixed and time-varying covariates. Fixed effects will consist of stratification factors (RPA class and prior therapy) and potentially other baseline covariates, such as KPS, DS-GPA grade, FLAIR volume change, and hippocampal volume. Since missing data is expected, patients with missing data will be compared to patients with complete data at each follow-up time with respect to baseline characteristics. If any of these characteristics are found to be significantly different, then they will be incorporated into the mixed effects model. 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).

Symptom Burden

Four subscales (symptom severity, symptom interference, neurologic factor, and cognitive factor score) as well as certain individual items (fatigue, neurologic factor items, and cognitive factor items) of the MDASI-BT will be analyzed. For discrete time point analyses, the change from baseline to each follow-up time point (2, 4, 6, and 12 months from the start of treatment) will be calculated and compared between treatment arms using a t-test or Wilcoxon-Mann-Whitney test, depending on the normality of the data.

Mixed effects models will be used to assess changes of the four subscale scores (symptom severity, symptom interference, neurologic factor, and cognitive factor score) across time using all available data while adjusting for stratification variables and other baseline characteristics. Since missing data is expected, it will be handled in a similar way as described for *Neurocognitive Function* above.

To assess the prognostic ability of baseline symptom severity, symptom interference, fatigue, neurologic factor items, and neurocognitive factor items on time to neurocognitive decline, the cause-specific Cox proportional hazards regression model will be used (Cox 1972).

Assessment of Quality Adjusted Survival

The VAS and index scores from the EQ-5D-5L will be calculated at each time point (baseline, 2, 4, 6, and 12, months from the start of treatment) and compared between treatment arms using a t-test with a 2-sided significance level of 0.05. If there are significant differences, then a cost analysis will be conducted.

Quality-adjusted survival (QAS) is defined by the weighted sum of different time

episodes added up to a total quality-adjusted survival time. A Markov model will be used to model cost for this analysis. The Medicare reimbursement in dollars/QAS will be calculated as a function of the monetary cost per relative value of each health state and its duration. The EQ-5D-5L index score at 6 and 12 months will be used for the cost-utility analysis. The z-test will be used to test the hypothesis that the cost-utility in the two treatment arms is the same with significance level of 0.05. The cost-utility using the Medicare reimbursement in dollars/QAS between the two treatment arms after adjusting for the baseline and stratification variables.

Overall Survival
Overall survival rates will be estimated using the Kaplan-Meier method (Kaplan 1958), and differences between treatment arms will be tested using the log rank test (Mantel 1966). Overall survival will be measured from the date of randomization to the date of death, or, otherwise, the last follow-up date on which the patient was reported alive. Of interest are survival rates at 6 and 12 months. These rates will be compared between arms using a Chi-square test. No treatment arm differences in overall survival are expected.

The Cox proportional hazard model (Cox 1972) will be performed with the stratification variables and other baseline characteristics as fixed variables to assess the treatment effect while adjusting for patient-specific risk factors.

Intracranial Progression
The occurrence of intracranial progression will be defined as progression in the brain or death. Intracranial progression will be assessed at the time of the primary endpoint analysis, which is expected to occur once all patients have 6 months of follow-up. MRI scans at baseline and 6 months will be reviewed to determine intracranial progression centrally. The 6 month comparison in intracranial progression rates between the treatment arms will be compared using a test of proportions. It is expected that the rates will be similar in both treatment arms.

Additionally, time to intracranial progression will be estimated using the Kaplan-Meier method (Kaplan 1958), and differences between treatment arms will be tested using the log rank test (Mantel 1966). Time to intracranial progression will be measured from the date of randomization to the date of intracranial progression, death, or, otherwise, the last follow-up date on which the patient was reported alive.

Progression in the parahippocampal regions also will be evaluated and reviewed centrally at 6 months. Few events are expected based on the results of RTOG 0933 where only 4.5% of patients experienced progression in this region (Gondi 2013; Gondi 2014). A test of proportions will be used to compare the rates in each treatment arm at 6 months.

Adverse Events
Adverse events (AE) will be evaluated using the CTCAE v4.0. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. The rate of all AEs related

to treatment and the rate of grade 3+ AEs regardless of relationship to treatment will be compared between treatment arms using a Chi-square test at a significance level of 0.05.

14.6.3 Power Calculations

Symptom Burden

The meaningful effect size for quality of life 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). Consensus from the literature seems to indicate that 0.5 SD is a conservative estimate of an effect size that is likely to be clinically meaningful. In the absence of other information, the 0.5 SD is a reasonable and scientifically supportable estimate of a meaningful effect. 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 meaningful (Sloan 2005). This discussion is very applicable to the MDASI-BT.

A two-sample t-test will be used with a 2-sided type I error of 0.05, there will be >90% statistical power to detect a medium effect size of 0.5 for a comparison of the change from baseline to 6 months from the start of treatment between the HA-WBRT and WBRT arms. To account for the multiplicity of the factor and individual item scores which are assumed to be correlated, Hochberg's method will be used (Hochberg 1988).

14.7 Exploratory Hypotheses and Endpoints

Correlation of Symptom Burden and Anxiety/Depression with Neurocognitive Function

An exploratory analysis, beginning with correlation coefficients, will be used to assess the association of symptom burden and anxiety/depression with neurocognitive function at each time point. The symptom burden items of interest are the "distressed (upset)", "sad", and "mood" items. From the EQ-5D-5L, the depression/anxiety item will be of interest.

Radiographic Evaluation

The effect of white matter injury and hippocampal volume (see Section 11.1 for more detail) on time to neurocognitive failure and baseline neurocognitive function will be examined. Both of these will be evaluated through MRI scans using physician-contoured and auto-contoured scores. Concordance rates will be assessed using Kappa statistics. The auto-contoured scores will be used for the remaining analyses due to the number of physicians reviewing the scans. White matter injury is measured by FLAIR volume change and is a continuous variable. Hippocampal volume is measured as a continuous variable also and both will be covariates considered in the Cox proportional hazards model to assess the impact on time to neurocognitive failure as described in Section 14.3.2 and the longitudinal modeling of neurocognitive function described in Section 14.6.2. Pearson correlation coefficients will be used to assess the effect of hippocampal volume and FLAIR volume change on baseline neurocognitive function, as measured by the HVLT-R, COWA, and TMT.

Effect of RTOG RPA and DS-GPA with Neurocognitive Function

Neurocognitive function, as measured by the HVLT-R, COWA, and TMT, will be correlated with both the RTOG RPA and the DS-GPA classification systems. In this

study, patients of RPA class I and II will be enrolled. Baseline neurocognitive function for each test will be compared between both RPA classes using either a t-test or Wilcoxon-Mann-Whitney test, depending on the normality of the data.

The DS-GPA classification system puts patients in a class from 0, worst prognosis, to 4.0, best prognosis as described in Appendix I; however, our eligibility criteria with respect to KPS makes a grade of 0 unattainable, resulting in only 4 classes (Sperduto 2011). Because only certain disease sites (non-small cell and small-cell lung cancer, melanoma, breast cancer, renal cell carcinoma, and GI cancers) can be classified into a DS-GPA grade, it is possible some patients may be excluded from this analysis. In RTOG 0933, lung, breast, and colon patients made up 75% of the patient population. A Spearman correlation coefficient will be used to assess the correlation between each baseline neurocognitive function test and DS-GPA class. Additionally, to describe the relationship of DS-GPA with changes in cognitive function over time, it will be included as a possible covariate in the modeling of cognitive function as described in Section 14.6.2.

14.8 Gender/Ethnicity/Race Distribution (24AUG2017)

No differences across patient subsets are anticipated.

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	17	9	26
Not Hispanic or Latino	269	215	484
Ethnic Category: Total of all subjects	286	224	**510**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	1	4	5
Asian	4	6	10
Black or African American	26	29	55
Native Hawaiian or other Pacific Islander	1	1	2
White	254	184	438
Racial Category: Total of all subjects	286	224	**510**

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APPENDIX I

DIAGNOSIS-SPECIFIC GRADED PROGNOSTIC ASSESSMENT (DS-GPA)

Non–small-cell and small-cell lung cancer

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

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma

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

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer

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

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma

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

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

GI cancers

Prognostic Factor	GPA Scoring Criteria 0	1	2	3	4	Patient Score
KPS	< 70	70	80	90	100	____

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2012;30(4):419-425.

Graded Prognostic Assessment (GPA) worksheet to estimate survival from brain metastases (BM) by diagnosis. Subtype: Basal: triple negative; LumA: ER/PR positive, HER2 negative; LumB: triple positive; HER2: ER/PR negative, HER2 positive. ECM, extracranial metastases; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky performance score; LumA, luminal A; LumB, luminal B; PR, progesterone receptor.

APPENDIX II (24AUG2017)

CERTIFICATION AND ADMINISTRATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY

STEP 1 – EXAMINER CERTIFICATION FOR NRG-CC001

Institutions with patients participating in the quality of life/neurocognitive function components of this study must meet certification requirements for administering neurocognitive assessments. The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study must be pre-certified by Dr. Wefel (See Section 8.3). Examiners who have completed the full certification procedure to perform these tests for RTOG 0825, 0834, 1114, NRG-BN001 or NRG-CC003 during the past 6 months do not need to complete the full certification procedure again, but the certification worksheet for NRG-CC001 must be faxed to Dr. Wefel for documentation purposes with information regarding the examiners prior certification (protocol number, date of certification). If these criteria are met, each examiner and NRG will be notified of the examiner's recertification status for NRG-CC001. Examiners who have not completed the full certification procedure for RTOG 0825, 0834, 1114, NRG-BN001 or NRG-CC003 within the past 6 months must complete the full certification procedure to be recertified to ensure continued familiarity with study procedures. All certified test administrators are required to attest to their proficiency in the language (English or French) in which the test is administered to the patient. Only certified test administrators proficient in the primary language of the patient are permitted to test the patient.

Prior to registering and/or testing a patient, potential examiners must:

1) Read the protocol
2) Read this Appendix (Certification and Administration Procedures for the Neurocognitive Test Battery)
3) Go to the NRG Oncology web site and use your username and password to access the link entitled, "Neurocognitive Training Procedure Letter" on the CC001 forms section of the NRG Oncology website. This letter will provide you with the web address and study specific password for the training video.
4) Obtain copies of the Neurocognitive Function Test packets (containing the HVLT-R, TMT and COWA), and the NRG-CC001 Blank Forms, pages 46-49 (containing the Neurocognitive Function Coversheet), and the Training Video Post Test from the NRG Oncology website
5) Watch the training video
6) Complete the Training Video Post Test
7) Complete a "practice" assessment with the Neurocognitive Function Test packet
8) Complete the Certification Worksheet (Appendix I)
9) All materials (i.e., Training Video Post Test, completed practice assessment and Neurocognitive Function Coversheet, certification worksheet) must be scanned and emailed (NeuropsychologyResearch@mdanderson.org) or faxed (713-794-4999) to Dr. Wefel, who will review it and correct any procedural errors with the trainee.
10) If the trainee demonstrates competency, he/she will be notified of the certification approval to administer the tests to study subjects as part of NRG-CC001. A certification

approval notice will be sent to NRG for the registration process and to ensure that only NRG-CC001-approved examiners are testing subjects on protocol NRG-CC001.

11) All neurocognitive materials for every patient at every time point must be uploaded to Medidata Rave® within 7 days after test administration.

STEP 2 – NEUROCOGNITIVE TEST PACKETS

Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. The tests have been grouped together in Packets that contain alternate versions of these neuropsychological tests. Please administer the tests in the order prescribed in the test packets. To ensure that the correct order is maintained per patient, please ensure that the NCF test packets are used in the order provided. If for any reason neurocognitive testing was not performed at an applicable patient visit, please use the next sequential packet at the next applicable visit (ie Patient Visit 1 = Packet 1, Patient Visit 2 = neurocognitive testing missed, Patient Visit 3 = Packet 2).

	Pre-Treatment Assessment	Month 2**	Month 4**	Month 6**	Month 12**
NCF Packet Label	Packet 1	Packet 2	Packet 3	Packet 4	Packet 5

**Neurocognitive testing should be performed as close to the day of the MRI as possible.

STEP 3 — TEST INSTRUCTIONS AND ADMINISTRATION PROCEDURES

Additional comments:

1. Testing must be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.
2. Tests should be administered in the following order to every patient and at every study visit: HVLT-R Part A (Trials 1-3); Trail Making Test Part A; Trail Making Test Part B; COWA; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition).
3. You may fill the delay interval between COWA and HVLT-R Part B (Delayed Recall) with QOL questionnaires.
4. Follow the instructions on the Forms Packet Index before submission of forms to NRG.
5. All neurocognitive materials for every patient at every time point must be uploaded to Medidata Rave® within 7 days after test administration. Please keep all original test forms. In the event of questions, contact Dr. Wefel. Results remain on file at the institution as source documentation pending request for submission by NRG or a study chair.
6. All test results are recorded on the Neurocognitive Function Coversheet, which is found in the Forms Packet. Study/case-specific labels must be applied to all forms.
7. Patients should not be given copies of their tests to avoid learning the material between test administrations.
8. Before dismissing the patient, thank the patient for his/her participation.
9. In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the Neurocognitive Function Coversheet.

1. HOPKINS VERBAL LEARNING TEST-REVISED (HVLT-R)

This test has three parts and six alternate forms:

Part A - Free Recall: Complete the three learning trials first

Part B - Delayed Recall: Complete after a 20 minute delay that includes administration of Trail Making Tests and COWA as well as the symptom self-report measures if appropriate

Part C - Delayed Recognition: Complete immediately after Delayed Recall

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2. <u>TRAIL MAKING TEST [Timed Test]</u>

<u>Part A – Sample</u>*:* The Sample for Part A must be completed/attempted by each patient and every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table).* Give the patient a <u>black pen</u> and say:

Examiner*: "On this page* (point) *are some numbers. Begin at number 1* (point to 1) *and draw a line from 1 to 2* (point to 2), *2 to 3* (point to 3), *3 to 4* (point to 4), *and so on, in order, until you reach the end* (point to the circle marked END). *Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample A correctly and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it.
The following explanations of mistakes serve as illustrations:

- ***"This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END"***

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
Examiner*: "Remember, begin at number 1 (*point to 1*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing <u>and</u> indicate the corresponding reason on the Trail Making Test Data Sheet and the <u>Neurocognitive Function Coversheet</u>. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

<u>Part A – Test</u>: After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:
Examiner*: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

- <u>Start timing as soon as the instruction is given to "begin"</u>
- Watch closely in order to catch any errors as soon as they are made. <u>If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred</u>

- The patient must complete the test in 3 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- If the patient does not complete the test within 3 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet and the Neurocognitive Function Coversheet indicating the reason the test was terminated and the last correct number reached on the test.
- If the patient successfully completes the test collect the worksheet and record the time to completion on the Trail Making Test Data Sheet and the Neurocognitive Function Coversheet in minutes and seconds. Then say, ***"That's fine. Now we'll try another one."***

Part B – Sample: The Sample for Part B must be completed/attempted by each patient and every assessment. Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:
Examiner*: "On this page (*point*) are some numbers and letters. Begin at number 1 (*point to 1*) and draw a line from 1 to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the end (*point to the circle marked END*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it.
The following explanations of mistakes serve as illustrations:

- ***"You started with the wrong circle. This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 (*point*) to A (*point*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, until you reach the circle marked END (*point*)"***

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
Examiner*: "Now you try it. Remember, begin at number 1 (*point to 1*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*) and so on, in order, until you reach the circle marked END (*point*). Ready, begin."*

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Test Data Sheet and the Neurocognitive Function Coversheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part B – Test:
After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

Examiner*: " Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (***point***) and draw a line from 1 to A (***point to A***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***), 3 to C (***point to C***) and so on, in order, until you reach the circle marked END (***point***). Remember, first you have a number (***point to 1***), then a letter (***point to A***), then a number (***point to 2***), then a letter (***point to B***), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred - do NOT start from the beginning
- The patient must complete the test in 5 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- Collect the worksheet and record the time to completion on the Trail Making Test Data Sheet in minutes and seconds
- If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Test Data Sheet and the Neurocognitive Function Coversheet indicating the reason the test was terminated and the last correct number or letter reached on the test.
- At the top of both Sample forms and both Test forms please write: patient initials, NRG case number, date of evaluation, institution name, name of certified tester, and the certified tester's phone number.

3. CONTROLLED ORAL WORD ASSOCIATION (COWA) [Timed Test]

This test has three parts (letters) and two alternate forms.

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APPENDIX III

Recursive Partitioning Analysis (RPA) System

Class I	1. KPS ≥ 70, 2. Primary controlled, 3. Age < 65, 4. Metastasis in brain only
Class II	KPS ≥ 70 and 1 of the following: • Primary uncontrolled • Primary controlled, age ≥ 65 • Primary controlled, age < 65, metastases in brain & other sites