A PHASE III TRIAL OF STEREOTACTIC RADIOSURGERY COMPARED WITH HIPPOCAMPAL-AVOIDANT WHOLE BRAIN RADIOTHERAPY (HA-WBRT) PLUS MEMANTINE FOR 5 OR MORE BRAIN METASTASES

CCTG, ALLIANCE, and NRG Oncology Protocol Number: **CE.7**

*Study Exempt from IND Requirements per 21 CFR 312.2(b)*

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This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by CCTG with the participation of the network of NCTN organizations: Alliance for Clinical Trials in Oncology; ECOG-ACRIN Cancer Research Group; and NRG Oncology, and SWOG.

**Participating Organizations**

**CCTG** / Canadian Cancer Trials Group (lead)

**ALLIANCE** / Alliance for Clinical Trials in Oncology

**ECOG-ACRIN** / ECOG-ACRIN Cancer Research Group

**NRG** / NRG Oncology

**SWOG** / SWOG Cancer Research Network

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*(For contact information of study personnel see Final Page.)*
CONFIDENTIALITY STATEMENT

This protocol contains information that is confidential and proprietary. The contents of this protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial may not be used for any other purpose and may not be disclosed to any other person or entity without the prior written permission of CCTG (and other applicable parties as designated by CCTG).
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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol and any supplementary information that may be added to this document, contains information that is confidential and proprietary and must be kept in confidence.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, in accordance with any modifications that may occur over the duration of the study, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to CCTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG with or without cause.

___________________________________________________
Qualified Investigator
(printed name and signature) Date

Protocol Number: CCTG CE.7

CENTRE: ________________________________
TREATMENT SCHEMA

This is an international multi-centre, open-label, randomized phase III trial comparing stereotactic radiosurgery (SRS) to hippocampal-avoidant whole brain radiotherapy (HA-WBRT) plus memantine in patients with 5 or more brain metastases.

Stratification

- DS-GPA predicted median overall survival [Sperduto 2012; Sperduto 2017] (< 6 months vs. ≥ 6 months)
- Use of targeted or immunotherapy within 4 weeks of original diagnosis of brain metastases, or planned for within 4 weeks of radiation therapy (yes or no)
- Histology (radio-resistant* vs. other)
- Metastasis within 5 mm of one hippocampus (yes or no)

* Radio-resistant is defined as brain metastases from a sarcoma, melanoma, or renal cell carcinoma histology.

Registration

Stratification Factors (collected at registration)

- DS-GPA predicted median OS (< 6 months vs. ≥ 6 months)
- Use of targeted or immunotherapy within 4 weeks of original diagnosis of brain metastases, or planned for within 4 weeks of radiation therapy (yes or no)
- Histology: radio-resistant vs. others
- Metastasis within 5 mm of one hippocampus: yes or no

Arm A

HA-WBRT 30 Gy in 10 fractions
+ memantine^{1}

Randomize 1:1

Arm B

SRS 18-20 or 22Gy in single fraction^{2}

Observation and Event Monitoring^{3}

1. Memantine will start the same day as HA-WBRT and must start no later than before the fourth HA-WBRT treatment. The target dose for memantine is 20 mg (10 mg divided twice daily). Dose will be escalated by 5 mg per week.

2. Lesions < 4 cc in volume will receive 22Gy while lesions 4-10 cc in volume will receive 18-20; details as outlined in the treatment section.

3. In the event of progressive brain metastases or systemic progression the patient remains under observation

N = 206
1.0 OBJECTIVES

1.1 Primary Objectives

- To compare the overall survival in patients with five or more brain metastases who receive SRS compared to patients who receive HA-WBRT plus memantine.

- To compare the neurocognitive progression-free survival in patients with five or more brain metastases who receive SRS compared to patients who receive HA-WBRT plus memantine.

1.2 Secondary Objectives

Patient/treatment Related Secondary Outcomes

- To compare time to central nervous system (CNS) failure (local, distant, and leptomeningeal) in patients who receive SRS compared to patients who receive HA-WBRT plus memantine.

- To evaluate if there is any difference in CNS failure patterns (local, distant, or leptomeningeal) in patients who receive SRS compared to patients who receive HA-WBRT plus memantine.

- To evaluate number of salvage procedures following SRS in comparison to HA-WBRT plus memantine.

- To evaluate the individual cognitive test results following SRS in comparison to HA-WBRT plus memantine.

- To tabulate and descriptively compare the post-treatment adverse events associated with the interventions.

- To evaluate the time delay to (re-)initiation of systemic therapy in patients receiving SRS in comparison to HA-WBRT plus memantine.

- To prospectively validate a predictive nomogram for distant brain failure [Ayala-Peacock 2014].

Economic Endpoints

- To compare the estimated cost of brain-related therapies in patients who receive SRS compared to patients who receive HA-WBRT plus memantine:
  - Comparison based on payer rates (Medicare for US / provincial healthcare authorities in Canadian jurisdictions with activity-based funding).

Quality of Life Endpoints

- To evaluate patient’s quality of life, as assessed by the EORTC QLQ-C30 + BN20, EQ-5D-5L, ECOG performance status, for those who receive SRS compared to those who receive HA-WBRT plus memantine.

Translational Endpoints

- Collect plasma to evaluate whether detectable somatic mutations in liquid biopsy can enhance prediction of the overall survival and development of new brain metastases.

- Analysis of serum samples for inflammatory biomarker C-reactive protein and brain-derived neurotrophic factor (BDNF) to elucidate molecular/genomic mechanisms of neurocognitive decline and associated radiographic changes.
**Imaging/Dosimetric Endpoints**

- Collect whole-brain dosimetry on all patients to be prospectively correlated with cognitive toxicity, intracranial control and radiation necrosis (hippocampal dosimetry will be retrospectively assessed).

- Collect imaging parameters and workflow details relating to the radiosurgery planning MRIs (including timing of MR prior to radiosurgery, magnet field strength, contrast type/dose/timing, use of image post-processing, and formal reviewed by radiology) to be prospectively correlated with tumour control outcomes (local control, intracranial control).

- Evaluate serial changes in imaging features found in routine MRI images (T2w changes, morphometry) that may predict tumour control and/or neurocognitive outcomes.
2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Study Rationale

The development of brain metastases is an unfortunate and common complication in oncology patients and can occur in 10–30% of cancer patients [Brown 2008]. The traditional treatment for many patients with brain metastases has been whole brain radiotherapy (WBRT), although stereotactic radiosurgery (SRS) has replaced WBRT as standard therapy for most patients with four or fewer brain metastases due to improved cognitive outcomes [Chang 2009; Brown 2016] and more favorable subacute health related quality of life [Soffietti 2013]. The M.D. Anderson trial of patients with 1 to 3 brain metastases found the mean posterior probability of decline for total recall at 6 months to be essentially at baseline function for SRS alone. Similarly, Alliance N0574 found better cognitive outcomes for patients with 1 to 3 brain metastases treated with SRS alone compared to SRS plus WBRT. On this phase III trial, cognitive deterioration at 3 months was 63.5% after SRS alone compared to 91.7% with SRS plus WBRT (p<0.001) [Brown 2016]. Additionally, multiple phase III randomized trials have shown that WBRT does not improve survival over SRS alone [Chang 2009; Brown 2016; Kocher 2011; Aoyama 2006]. Results from a recent Japanese phase II study suggest that SRS alone is feasible in patients with up to 10 brain metastases [Yamamoto 2014]. Radiosurgery for as many as 15 brain metastases has been found to be safe, notably in a series of 360 patients from Japan [Yamamoto 2014]. Radiosurgery for more than 15 mets has also been found to be feasible and safe [Benjamin 2021; Mizuno 2019; Nguyen 2019].

However, studies demonstrating inferior cognitive outcomes following upfront WBRT relative to upfront SRS for 1-4 brain metastases were largely conducted prior to the publication of large brain metastasis trials testing pharmacologic and technologic neuroprotective strategies during WBRT and leading to the safer delivery of WBRT.

Memantine is an NMDA receptor antagonist shown to be neuroprotective in pre-clinical models [Pellegrini 1993]. Memantine was studied in a placebo-controlled, double-blind, randomized trial in patients with brain metastases receiving WBRT (RTOG 0614) [Brown 2014]. Patients received WBRT and were randomized to receive placebo or memantine during and after WBRT for a total of 24 weeks. Between 2008 and 2010, 554 patients were accrued. 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. Although the difference in the primary endpoint (decline in HVLT-R DR at 24 weeks) did not quite reach statistical significance (p = 0.059), this may be attributable to the fact that there were only 149 analyzable patients at 24 weeks compared with an expected 442 evaluable cases in the protocol. This resulted in only 35% statistical power to detect the absolute 0.87 difference in HVLT-R DR decline hypothesized in the protocol. Patients in the memantine arm did however have a significantly longer time to cognitive decline (HR 0.78; 95% CI, 0.62 to 0.99; p=0.02). These practice-changing results led to the establishment of prophylactic memantine as standard of care during WBRT.

RTOG 0933 was a phase II trial of conformal avoidance of the hippocampus during WBRT using intensity-modulated radiotherapy (IMRT) for patients with brain metastases (15). This trial demonstrated highly promising cognitive outcomes relative to historical controls and served as the basis for NRG CC001, a phase III trial of WBRT with memantine with or without hippocampal avoidance during WBRT for patients with brain metastases.
The following are preliminary results presented at the 2018 Annual Meetings of the American Society for Radiation Oncology (ASTRO) and during the plenary session of the 2018 Annual Meeting of the Society for Neuro-Oncology (SNO). NRG CC001 reached its target accrual in March 2018 with 518 patients randomized. Median age was 61.5 years, with the majority of patients having non-small cell lung cancer as primary tumor (57.7%) and recursive partitioning analysis (RPA) class II (86.3%). There was no difference in any, treatment-related, or grade 3 or higher toxicity between the WBRT plus memantine and HA-WBRT plus memantine arms. The median follow-up for all alive patients was 7.89 months. There was no statistically significant difference between arms in terms of baseline cognitive function, overall survival (HR=1.13, 95% CI: 0.90-1.41, p=0.31) or intracranial progression-free survival (HR=1.14, 95% CI: 0.93-1.41, p=0.21).

Hippocampal avoidance during WBRT plus memantine prevented cognitive failure (HR=0.74, 95% CI: 0.58-0.95, p=0.020). The difference was seen first at 4 months with a cognitive function failure rate of 62.7% (95% CI: 55.6-69.0) in the WBRT plus memantine arm compared to 54.5% (95% CI: 47.1-61.3) for the HA-WBRT plus memantine arm. The cognitive preservation benefit of hippocampal avoidance was independent of age and attributed to less deterioration in executive functioning (assessed using the Trail Making Test B) at 4 months and less deterioration in immediate recall and recognition (assessed using the Hopkins Verbal Learning Test-Revised) at 6 months. Additionally, analyses of patient-reported outcomes (assessed using the M.D. Anderson Symptom Inventory Brain Tumor Module) demonstrated improvements in perceived cognition, fatigue, and symptom interference with activities of daily living at 6 months in the HA-WBRT plus memantine arm. Improvements in patient-reported cognition were attributed to improvements with difficulty speaking and problems remembering things.

The study demonstrated prevention of cognitive failure and preservation of patient-reported symptoms with hippocampal avoidance and has advanced our approach to safer delivery of WBRT.

The question of whether SRS or HA-WBRT plus memantine is the optimal modality in patients with five or more brain metastases is significant from a societal and medical resources standpoint since the charges related to SRS and IMRT for HA-WBRT can be considerably higher than those of conventional WBRT [Brown 2008, Brown 2009].

However, examining therapy-associated costs is particularly complex in patients with multiple brain metastases, because such patients are likely to undergo additional salvage procedures for new brain metastases. Therefore, the additional costs of salvage are also important to incorporate into economic comparisons, especially when SRS is anticipated to result in higher intracranial relapse rate and need for salvage therapies [Chang 2009; Brown 2016; Kocher 2011; Aoyama 2006].
The significance of the proposed examination is underscored by quickly growing support of SRS in the community for this patient population, even despite the ongoing uncertainties about the true cost burden of SRS vs WBRT (HA-WBRT or conventional WBRT) from payer and provider perspectives, as well as uncertainties about the comparative risk/benefit of these strategies for survival, CNS control, quality of life, and neurocognitive function in patients with five or more metastases. Several series have already suggested value of SRS in improving cost utility in the population of 4 or fewer brain metastases. Lal et al. reported a cost-effectiveness analysis of a randomized trial of SRS vs SRS + WBRT for 1-3 brain metastases and found that SRS alone had a higher average cost but was associated with an improvement in QALYs with an incremental cost-effectiveness ratio of $41,783 per QALY [Lal 2012]. Savitz et al performed a cost-effectiveness analysis using a Markov model and found that SRS was a cost effective treatment option, even in patients who had prognoses of six months or less [Savitz 2015]. Importantly, none of these studies accounted for the cognitive preservation benefits or costs of modern neuroprotective strategies of hippocampal avoidance using IMRT and memantine during WBRT. Accordingly, it is imperative that SRS versus HA-WBRT plus memantine for five or more brain metastases is studied in a prospective multi-institutional cooperative group trial to evaluate the cost, as well as the cost-effectiveness and cost utility of these modalities in this population.

Recently a multi-institutional nomogram was developed to predict the development of new brain metastases after primary SRS without WBRT [Ayala-Peacock 2014]. This tool was intended to aid practitioners in determining the proper patient population for the use of SRS vs HA-WBRT plus memantine with the assumption that patients with predicted rapid brain failure after SRS may be better candidates for HA-WBRT plus memantine. A major finding in the nomogram study was that the nomogram was superior to simply using the number of metastases in predicting the development of new brain metastases and thus the potential need for early HA-WBRT plus memantine [Ayala-Peacock 2014]. As part of the proposed study, we plan to perform a prospective validation of the nomogram’s performance and of the cost-effectiveness of potential strategies incorporating the nomogram in clinical decision-making.

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<tr>
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<th>Distant Failure (1 yr)</th>
<th>Overall Survival (1 yr)</th>
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<td>WBRT</td>
<td>71%</td>
<td>33%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>WBRT + SRS</td>
<td>82%</td>
<td>27%</td>
<td>29%</td>
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<tr>
<td>EORTC 22952 [Kocher 2011]</td>
<td>SRS</td>
<td>70%</td>
<td>44%</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td>SRS + WBRT</td>
<td>87%</td>
<td>28%</td>
<td>46%</td>
</tr>
<tr>
<td>MDACC [Chang 2009]</td>
<td>SRS</td>
<td>67%</td>
<td>55%</td>
<td>60%</td>
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<tr>
<td></td>
<td>SRS + WBRT</td>
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<td>27%</td>
<td>21%</td>
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<tr>
<td>JROSG-99-1 [Aoyama 2006]</td>
<td>SRS</td>
<td>76%</td>
<td>63%</td>
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<tr>
<td></td>
<td>SRS + WBRT</td>
<td>90%</td>
<td>42%</td>
<td>39%</td>
</tr>
<tr>
<td>Alliance N0574 [Brown 2016]</td>
<td>SRS</td>
<td>73%</td>
<td>30%</td>
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<tr>
<td></td>
<td>SRS + WBRT</td>
<td>90%</td>
<td>8%</td>
<td>36%</td>
</tr>
</tbody>
</table>
2.2 Current Clinical Trial Relevance and Potential Impact

A trial comparing SRS to WBRT for patients with greater than 5 brain metastases was initiated by the North American Gamma Knife Consortium. Although this trial was of interest, it was limited in its scope to only one of the several radiosurgical platforms and limited in its statistical power (39 patients planned to be accrued per treatment arm) and the trial closed long before reaching the total target accrual [personal communication - Dr Igor Barani, trial co-chair]. The currently proposed study is being co-lead by the Alliance, NRG Oncology, and CCTG, both of which have shown an ability to accrue to large brain metastasis studies in the cooperative group setting. In addition, by allowing multiple SRS platforms and a greater diversity of institutions to accrue, the proposed study provides a more representative sample of patients and practice patterns. Lastly, the quality assurance infrastructure critical to the conduct and positive results of RTOG 0933 and NRG CC001 will be carried forward to this trial.

As outlined above, the proposed trial could have significant financial and clinical implications on patient cognitive function, overall survival, QOL and cost of treatment. As an example, if overall survival were significantly worse with SRS, this would dampen enthusiasm for SRS and hence decrease utilization of an expensive modality that may require multiple applications to treat brain disease; this would also establish primary HA-WBRT plus memantine as the standard of care for patients with 5 or more brain metastases. If the SRS cohort had a superior outcome in neurocognitive function, QoL, and/or overall survival compared to HA-WBRT plus memantine, it would establish SRS as the standard of care for patients with five or more brain metastases. If there was a mixed result with significantly higher cost, but better neurocognitive function with SRS, this issue may remain controversial but there would be high level evidence to assist in making therapeutic decisions. Prospective data will be available to generated hypotheses as to which groups would be best suited for each therapy. Prospective randomized trials have previously dramatically shaped the usage of SRS. The Alliance N0574 study has contributed to SRS without WBRT becoming the standard of care for patients with 1-4 brain metastases. On the other hand, the negative RTOG 93-05 study of radiosurgery in glioblastoma led to a dramatic decrease in the use of SRS boost in the treatment of glioblastoma multiforme [Souhami 2004]. A randomized trial such as the one proposed can best provide the high level evidence necessary to help inform the usage of SRS in this population.

Below is a table that outlines the previously reviewed series of patients with greater than 5 brain metastases treated with SRS.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of metastases</th>
<th>No. of patients</th>
<th>1 Year Intracranial Failure</th>
<th>Overall Survival (mth.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamamoto (2014)</td>
<td>2-9</td>
<td>360</td>
<td>35%</td>
<td>6.8</td>
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<tr>
<td>Yamamoto (2014)</td>
<td>5-10</td>
<td>208</td>
<td>64%</td>
<td>10.8</td>
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<td>Chang (2010)</td>
<td>6-10</td>
<td>58</td>
<td>66%</td>
<td>10</td>
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<tr>
<td>Ayala-Peacock (2014)</td>
<td>5-10</td>
<td>125</td>
<td>49%</td>
<td>6.2</td>
</tr>
<tr>
<td>Hunter (2012)</td>
<td>5-10</td>
<td>64</td>
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</tr>
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<td>Serizawa (2010)</td>
<td>5-6</td>
<td>93</td>
<td>49%</td>
<td>7.1</td>
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<td></td>
<td>7-10</td>
<td>122</td>
<td>34%</td>
<td>7.4</td>
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<tr>
<td>Raldow (2012)</td>
<td>5-10</td>
<td>84</td>
<td>62%</td>
<td>7.6</td>
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<tr>
<td>Rava (2013)</td>
<td>10-17</td>
<td>53</td>
<td>10%</td>
<td>6.5</td>
</tr>
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<td>Yamamoto (2014)</td>
<td>11-15</td>
<td>360</td>
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<td>Nguyen (2019)</td>
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<td>NA</td>
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<tr>
<td>Benjamin (2021)</td>
<td>25 or more</td>
<td>95</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
2.3 **Neurocognitive and Quality of Life (QOL) Measures**

The current trial will build on the success of N0574, NRG Oncology CC001, and N107C/CEC.3 utilizing many of the same QOL and neurocognitive measures.

**Neurocognitive Evaluation**

The prevention and palliation of neurologic problems due to progression are important goals of treatment. Improvement in survival in isolation is not an ideal measure of the benefit of a local therapy for brain metastases, as overall survival may be limited by extracranial disease [Mehta 2009; Meyers 2006]. Measurement of neurocognitive function with an established battery by a qualified examiner is an *objective* measure akin to other objective measures such as imaging or laboratory evaluation. The US Food and Drug Administration has indicated that "improvement in neurocognitive function or delay in neurocognitive progression are acceptable end points" [Meyers 2006]. Neurocognitive function as a primary endpoint has become an accepted practice and has been utilized in a number of ongoing and completed phase III trials [Chang 2009; Mehta 2009]. Therefore, as with N0574, CC001, and N107C/CEC.3, neurocognitive progression will be a primary endpoint.

The neurocognitive tests to be used in this study, the same tests as N0574 and NRG CC001, were chosen on the basis of accepted standardization and psychometric principles, published normative data relative to routine demographics, relevance to general neurocognitive status, and brevity of the overall battery. The tasks selected have either low associated practice effect or include multiple equivalent formats. In addition, similar variations of this battery have been utilized in multiple multi-institutional trials including N0574, N0577, E3F05, RTOG 0614, and the two phase III randomized motexafin gadolinium studies [Mehta 2009, Meyers 2004]. The tests include:

- Memory (5 minutes): Hopkins Verbal Learning Test (HVLT) [Brandt 1991].
- Fluency (5 minutes): Controlled Oral Word Association Test from the Multilingual Aphasia Examination (COWAT) [Benton 1978].
- Visuomotor speed and attention: Trail Making Test A (3 minutes) [Reitan 1958].
- Executive function: Trail Making Test B (5 minutes) [Reitan 1958].
- Delayed Memory (5 minutes): Recall and Recognition of Word List encoded from the HVLT

**Quality of Life**

Quality of life is a multidimensional construct, which can be defined as a state of general well being reflecting physical, psychological, and social well being and the control of disease and/or treatment related symptoms. The aspects of quality of life that are most likely to be affected in this study are treatment related symptoms and overall quality of life.

Quality of life will be evaluated in all patients entered in the study. Assessments will consist of a self-administered questionnaire. In this study, the EORTC core questionnaire QLQ-C30, in conjunction with the brain module QLQ-BN20, will be used. Patient performance status, and the EQ-5D-5L questionnaire will also be used to evaluate quality of life.
Since mood disturbances may influence cognitive function, it is important to interpret QOL data in light of the neurocognitive tests. The EORTC QOL questionnaire core-30 (QLQ-C30, version 3); and the EORTC QOL questionnaire – brain module (QLQ-BN20) have both robust psychometric properties as a result of rigorous testing and development from their use in several international clinical trials of cancer and are highly consistent across different language-cultural groups. The EORTC QLQ-C30 consists of 30 questions which comprise five function scales: physical, role (related to interference of disease with family life or social activities), emotional, cognitive, and social; six single-item scales including dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial effect of tumour and treatment; and overall QOL. EORTC QLQ-BN20 is designed for use with patients with brain tumours undergoing chemotherapy or radiotherapy and has 20 items that assesses visual disorders, motor dysfunction, communication deficit, various disease symptoms (e.g. headaches and seizures), toxic effects of treatment (e.g. hair loss), and future uncertainty.

2.4 Health Economics Rationale

An empiric cost-effectiveness analysis comparing SRS or HA-WBRT plus memantine in patients with 5 or more metastases will provide critical knowledge to support best practice dissemination of these treatment strategies. Cost-effectiveness data will allow for pragmatic, long-term application of our results that allows for sustainable access to high-value treatment, as presently, there are few data to inform a strategic treatment approach for this patient group.

A prior Markov-based modeling study compared cost effectiveness of SRS vs. WBRT in patients with 2-10 brain metastases [Lester-Coll 2016]. In this analysis, the incremental cost effectiveness ratio (ICER) of SRS vs. WBRT was $123,256—a result considered intermediate in the range of accepted cost-effectiveness thresholds between $50,000 and $150,000 per QALY [ICER Review 2017]. Nevertheless, the actual cost effectiveness of SRS is sensitive to 1) actual variations in costs to deliver SRS; 2) actual utilities (patient preferences) associated with the individual treatments as well as subsequent salvage therapies, progression, neurologic dying, cognitive decline, and major treatment toxicities; and 3) the number of brain metastases or other clinical factors that modify risks of relapse, salvage, and overall survival. The above study, based on a theoretical model, was limited in quantifying such factors. Furthermore, the above study was limited by the dearth of cost, cost-effectiveness, and utilities data for patients with more than 10 brain metastases, due to their lack of inclusion in available prospective trials of SRS [Yamamoto 2014]. Lastly, the above study did not account for the costs and cognitive preservation benefits of hippocampal avoidance using IMRT or prophylactic memantine.

Accordingly, our trial will provide a unique opportunity to empirically address these scientific gaps. Nuanced cost data will be established by our analysis based on a range of payer-perspective costs from two established systems (Medicare and Canadian provincial health authorities funding), and this information may be critically important for informing strategic, value-based delivery of the treatment options [Lester-Coll 2016]. Additionally, nuanced utilities data will be collected on all patients at multiple time points reflecting the key health states, especially with salvage and cognitive decline. Despite the fundamental sensitivity of cost-effectiveness assessments to variations in health utilities, the current assumptions for utilities in patients with brain metastases are based on an extremely limited number of patients. For example in a contemporary hallmark prospective study of utilities, only 24 patients were included [Lester-Coll 2016]. Therefore, our prospective data collection of this measure will be substantially additive. Finally, inclusion of patients’ baseline clinical nomogram will help demonstrate how clinical features modify the relative cost-effectiveness of SRS or HA-WBRT plus memantine, providing, in total, a comprehensive understanding of the clinical, cost, and utility aspects comparing SRS or HA-WBRT plus memantine.
Measures

EQ-5D-5L

The EuroQol five-dimension (EQ-5D-5L) questionnaire provides estimates of health-related utility required in the incremental cost (ICER) per quality-adjusted life-year (QALY) framework. This is the current preferred framework for assessing cost-effectiveness and value by the Institute for Clinical and Economic Review [ICER Review 2017] and the National Institute for Health and Clinical Excellence (NICE) [Longworth 2013].

The EQ-5D-5L is a validated health-related quality of life (HRQOL) questionnaire, encompassing patients’ self-reported holistic view of health, physical, emotional, and social functioning, including both positive and negative aspects. It focuses on five dimensions, mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which is summarized in a health state that can be converted into a single index value [Euroqol].

2.5 Imaging Sub-Study Rationale

Impact of the Quality of Image Acquisition and Utilization on Outcomes

The MR imaging protocol can impact the ability to detect and target small brain metastases [Garcia 2016; Lee 2016]. Higher spatial resolution, magnet strength, and gadolinium contrast dose or contrast agent relaxivity can lead to the detection of additional small brain metastases [Garcia 2016; Huang 2010; Kim 2010]. Leaving undetected small brain metastases untreated will intuitively impact intracranial control following radiosurgery alone. The success of highly conformal radiation delivery achieved with radiosurgery relies on accurate targeting, which in turn depends on the geometric accuracy of the images used for targeting. Variations in the MR imaging parameters can impact the associated spatial distortions in the images, which may lead to missing all or part of the tumour [Karaiskos 2014]. Therefore, determining the imaging parameters that may impact outcome and optimizing these to ensure appropriate patient selection and treatment would be valuable. In this study, we will evaluate the impact of the imaging parameters and imaging workflow on outcomes including local and intracranial control. This includes the spatial resolution of the acquired images, magnet strength, and gadolinium contrast dose or contrast agent relaxivity, and having a dedicated neuroradiologist interpretation of a treatment planning MRI can lead to the detection of additional small brain metastases and impact outcomes including local and intracranial control.

Imaging Measures

The purpose of this sub-study is to identify the combination of imaging parameters and workflow aspects that have the highest accuracy in detection of small brain metastases. Image acquisition will be done prospectively, though image analysis will be performed in a retrospective manner. Minimum parameters and recommended imaging protocols for the planning MRI brain scan and follow-up MRI brain scans are outlined in Appendix IX, and will include:

(i) Axial post-contrast images.
(ii) 2 mm or less slice thickness (1mm thickness for 3D T1w IR-GRE).
(iii) Scanner should be at least a 1.5 Tesla magnet with single dose contrast (higher dose permitted if standard at the institution).
(iv) Acquisition at most 14 days prior to treatment.
It will be recommended that the same technique be used for each of the diagnostic MRI brain scans at follow-up.

The presence or absence of occult small brain metastases will be confirmed on subsequent follow-up MRI brain scans (i.e. if a lesion is suspicious but becomes larger on subsequent MRI, it is concluded to have been a metastasis on the prior scan).

*Imaging Biomarkers Associated with Cognitive Toxicity from Brain Radiation*

It has been documented that after both external beam and stereotactic radiation to the brain, radiographic changes are noted on brain MRI \[\text{Tomura 2006; Curnes 1986}\]. White matter changes have been shown to be more prevalent following whole brain radiation compared with radiosurgery alone; however the clinical impact of these radiographic changes is not entirely clear \[\text{Trifiletti 2015; Cohen-Inbar 2016}\]. Changes in brain volume have been identified as potential predictive imaging biomarkers for functional changes \[\text{Chang 2014; Foster 2006}\]. Changes in volume of the brain and various substructures have been observed following radiotherapy \[\text{Agbahiwe 2017}\].

On conventional MRI, changes in the following measures will be correlated with neurocognitive function:

(i) magnitude and rate of change in the volume of T2 hyperintensity;
(ii) baseline and changes in volume of the brain and subvolumes (e.g. hippocampus, frontal lobe, temporal lobe) over time.

*Dosimetry and Cognitive Toxicity*

Studies have reported a relationship between the radiation dose and irradiated volume with the incidence and severity of radiation toxicity. Irradiation of specific subregions of the brain including the hippocampus and cerebellum have been specifically associated with cognitive toxicity \[\text{Merchant 2014; Gondi 2013}\].

For all patients imaging used for planning (CT and/or MRI) will be collected as well as associated dosimetry. This will allow investigation of dosimetric parameters correlated with tumour control (which can be based on uniform target segmentation). It will also allow correlative evaluation of radiation dosimetry to the brain and its substructures with cognitive outcomes.

2.6 Correlative Research Rationale

Buffy coat (i.e. white blood cells), plasma, serum, and urine will be collected during this trial at baseline, immediately after RT, and at 8 weeks, 4, 6, and 12 months. The proposed multiple molecular/genomic assays will include: (1) liquid biopsies of circulating cell-free DNA (cfDNA) and circulating tumour cells (CTCs); (2) plasma; and (3) urine.
The **primary goal** is to evaluate whether molecular/genomic biomarkers (i.e. somatic mutations) in liquid biopsy can enhance prediction of the overall survival and development of new brain metastases in patients with five or more brain metastases who receive SRS compared to patients who receive HA-WBRT plus memantine. Under the overall null hypothesis that both treatments have similar clinical outcomes, we hypothesize that patients with worse molecular genomics at baseline or follow-up visits (and/or changes from baseline), may predict clinical outcomes within each treatment arm and identify clinically actionable mutations. The results from a recent study showed that cfDNA from metastatic cancer patients can identify clinically actionable mutations distinct from primary tumours \[Butler 2015\].

The **secondary goal** is to evaluate differences of molecular genomics (i.e. somatic mutations) of liquid biopsy samples at baseline and changes by primary tumour sites. Brain metastases usually start out as primary cancers of the lung, breast, melanoma, and others. With current scientific knowledge of these primary cancer sites and metastatic tumours \[Pan 2015\], we hypothesize that there are specific and shared somatic mutations in cfDNA and primary tumour sites.

The **tertiary goal** is to investigate molecular/genomic mechanisms of neurocognitive decline and radiographic changes. Building on the concept that RT has direct killing and indirect effects on tumour cells by triggering immune/inflammatory responses, our working hypothesis is that changes of circulating immune/inflammatory biomarkers can predict treatment-related neurocognitive decline and radiographic changes.

**Circulating Cell-Free Tumour DNA (cfDNA)**

It has been established for many years that tumour DNA is shed into the blood and it can be detected as cfDNA in plasma. Quantification and characterization of cfDNA has the potential to revolutionize cancer detection, treatment response assessment, tumour burden determination, and tumour progression monitoring. The isolation of cfDNA is quite straightforward. The levels of ctDNA increase or decrease may reflect tumour burden, and cfDNA contains somatic mutations found in both primary and metastatic lesion \[Abbosh 2017; Yi 2017\]. More importantly, the capacity to screen for cfDNA in serial liquid biopsies offers the possibility to monitor tumour progression, responses to therapy, and influence treatment decisions that ultimately may improve survival \[Chaudhuri 2015\]. In a combined analysis of thirty-nine studies with 4,052 cancer patients, cfDNA detection was associated with worse overall survival \[Ocana 2016\]. Considering brain metastases start out as primary cancers of the lung, breast, melanoma, and others, we anticipate that there are specific and/or enriched somatic mutations in cfDNA that may reflect chemo or radio-resistant tumour phenotype of the primary cancer sites and metastatic tumours. Therefore, our first correlative research rationale is that quantitation of cfDNA levels and somatic mutation profiles may enhance prediction of RT responses, development of new brain metastases, and overall survival.

Plasma samples will be stored and used for Guardant360 cell-free DNA (cfDNA) assay for somatic mutations detection with digital sequencing methodology. As stated in a previous study of 365 true positives and a single false positive in a cumulative targeted region of 1.56 million base pairs, the analytic specificity is at 99.9999% or a 0.0001% false positive rate \[Pareira 2017; Lanman 2015\]. It was concluded that the diagnostic accuracy was at 99.9999%, analytic sensitivity was at 100% (95% CI 98.9944%–100%), and the analytic specificity was at 99.9999%. Regardless, we usually run duplicate assays on 10% samples to validate study findings.
C-Reactive Protein (CRP) and Brain-derived Neurotrophic Factor (BDNF)

RT may lead to inflammatory response and decreased BDNF that may impact neurocognitive and QOL of patients with brain metastases. Increased serum CRP level reflect elevated systemic/peripheral inflammation. However, in animal model, CRP is associated with brain neuro-inflammatory response in response to ionizing radiation [Gupta, 2017]. In humans, the results of two studies suggest that CRP was associated with neuro-inflammatory state of amyotrophic lateral sclerosis and late-life depression [Lunetta, 2017; Su, 2016]. CRP was associated with cognitive function in post-menopausal women [Bojar, 2016]. Elevated RT-induced CRP was associated with skin toxicity in breast cancer [Rodriguez-Gil, 2014]. Therefore, our second correlative research rationale is that serum CRP levels may serve as a neuro-inflammatory biomarker for neurocognitive and QOL measures. BDNF is an important neurotropic factor derived from brain. A significant decrease of BDNF concentration was associated with fatigue in prostate cancer receiving external beam RT [Saligan, 2016]. In animal model, memantine treatment increased BDNF protein levels in the prefrontal cortex in stressed rats [Reus, 2012]. However, there is no prior study evaluating the effects of memantine on BDNF in humans. Therefore, our third correlative research rationale is that memantine in Arm A may increase BDNF levels that are related to neurocognitive and QOL measures.

With limited access to primary and metastatic brain tumours, the proposed liquid biopsy-based laboratory assays aim to evaluate effects of RT on cancer cells and immune/inflammatory responses [Rodriguez-Gil, 2014; Bhattacharyya, 2016; Saba, 2016]. The scientific knowledge gained from the biomarker research will identify actionable mutations and targets for precision medicine/intervention to improve RT efficacy and minimize RT-related neurocognitive decline [Poleszczuk, 2016; Chargari, 2016].

With anticipated limited amounts of DNA that can be obtained from cfDNA and CTC, we will apply a focused next-generation sequencing approach using the Qiagen Human Comprehensive Cancer GeneRead DNAseq Targeted Panel V2 (Qiagen) with 10 ng DNA input. This panel targets the enrichment of the coding (exonic) regions of 160 cancer-related genes that are most commonly mutated in cancers with a recognizable oncogenic consequence. This panel covers 20 genes commonly mutated in lung cancer (MTOR, NRAS, PTGS2, PTEN, HRAS, KRAS, RB1, AKT1, TP53, ERBB2, STK11, ALK, CTNNB1, PIK3CA, PDGFRA, KIT, EGFR, MET, BRAF, CDKN2A) and 44 genes most commonly mutated in human breast cancer samples (ACVR1B, AKT1, ATM, BAP1, BRCA1, BRCA2, CBFB, CDH1, CDKN2A, EGFR, EP300, ERBB2, ERBB3, ESRI, EXOC2, EXT2, FBXO32, FGFR1, FGFR2, GATA3, IRAK4, ITCH, KMT2C, MAP2K4, MAP3K1, MDM2, MUC16, MYC, NCOA1, NEK2, PBRM1, PCDG2, PIK3CA, PIK3R1, PPM1L, PTEN, PTGFR, RB1, RET, SEPT9, TP53, TRAF5, WEE1, ZBED4). More importantly, this panel also covers mutations of 24 clinically-relevant genes identified by guidelines and published opinions from groups such as the National Comprehensive Cancer Network (NCCN), College of American Pathologists (CAP), and American Society of Clinical Oncology (ASCO). These 24 genes include AKT1, ALK, AR, BRAF, CTNNB1, DDR2, EGFR, ERBB2, FGFR3, GNA11, GNAQ, IDH1, IDH2, KIT, KRAS, MAP2K1, MET, NRAS, PDGFRA, PIK3CA, PTEN, RET, STK11, and TP53. Next generation sequencing (NGS) will be carried out using an Illumina MiSeq desktop sequencer. Qiagen Cloud-Based DNAseq Sequence Variant Analysis software will be used to analyze the GeneRead NGS data according to the manufacturer’s instructions. Final somatic mutation data will be merged with clinical data for subsequent statistical analysis.

Urine Samples

Urine samples will be stored and used for future studies of radiotherapy-related changes of metabolomics and oxidative DNA damage, such as 8-hydroxydeoxyguanosine (8-OHdG).
3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Memantine

3.1.1 Name and Chemical Information

- Common Name: Memantine Hydrochloride
- Common Trade Name: Med-Memantine (Namenda)
- Chemical name: 1-amino-3,5-dimethyladamantane hydrochloride
- Molecular formula: C_{12}H_{21}N.HCl
- Molecular weight: 215.77 (hydrochloride), 179.31 (base)

3.1.2 Chemical Structure

![Chemical Structure of Memantine](image)

3.1.3 Mechanism of Action

Memantine hydrochloride belongs to the low to moderate affinity, non-competitive N- methyl-D-aspartate (NMDA) receptor antagonist class of drugs. Persistent activation of NMDA receptors by glutamate was believed to contribute to the symptoms of Alzheimer's disease. Abnormal transmission of nerve signals through NMDA-receptors in the brain may affect memory and other mental functions, and contribute to Alzheimer's disease.

Memantine hydrochloride inhibits the excitotoxic action of glutamate by blocking the NMDA receptor. This prevents exposure of the neuron to an excessive influx of calcium, which is thought to be one of the mechanisms responsible for neuronal death. Memantine hydrochloride, while blocking NMDA under pathologic conditions, rapidly dissociates from the receptor during the normal phasic activity required for learning and memory. It showed low to negligible affinity for GABA, benzodiazepine, dopamine, adrenergic, histamine and glycine receptors and for voltage-dependent Ca^{2+}, Na^{+} or K+ channels. The action of memantine on NMDA-receptors may help normalize the transmission of nerve signals, which may help slow the decline in some of the symptoms of Alzheimer disease.

3.1.4 Experimental Antitumour Activity

Memantine does not exhibit antitumour activity. It may be useful as monotherapy for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimers type (i.e. stabilization or less worsening of functional and cognitive symptoms).
3.1.5 **Animal Toxicology**

Standard safety pharmacology studies were conducted to evaluated memantine’s effects on CNS, cardiovascular, gastrointestinal and renal functions. At doses higher than the pharmacologically relevant dose (≥ 30 mg/kg), memantine produced considerable CNS side effects. Decreased awareness, motor activity and reflexes were observed at high doses (100 mg/kg). High doses of memantine (≥ 30 mg/kg, intraduodenal) decreased cardiac minute output, stroke volume and systolic left ventricular pressure. Memantine inhibited intestinal motility in rats with an ED50 of 20 mg/kg, and produced diuresis and saluresis in rats at high doses (40 mg/kg; p.o).

Acute oral and intravenous toxicity studies in rats and mice demonstrate that memantine is moderately toxic. The lowest lethal dose is ≥ 300 mg/kg in both species. Toxic symptoms were similar by all administration routes: ataxia, tremor, prone position and bradypnea. These motor effects at high doses are consistent with central nervous system blockage of glutamatergic transmission in neocortex and cortical projection fields. Recovery was relatively rapid in all cases, and no persistent clinical signs were seen in survivors 14 days after acute high dose treatment.

In subchronic and chronic studies the most prominent clinical signs in all species were related to the central nervous system and included ataxia, tremor, unsteadiness and aggressiveness or hyperexcitability in rodents, incoordination, tremors and apathy or quietness in dogs and baboons, and convulsions in dogs. Reduced body weight, which was sometimes accompanied by a change in food consumption, was noted in some studies.

Pathological changes, such as accumulation of foamy macrophages in several tissues, renal papillary mineralization, tubule-interstitial nephritis, vacuolization of defined cortical neurons, and corneal opacities were observed in repeat-dose toxicity studies in rodents.

3.1.6 **Phase III Trials**

A phase III trial was conducted by the NRG (the RTOG) to determine the protective effects of memantine on cognitive function in patients receiving whole-brain radiotherapy (WBRT). Adult patients with brain metastases received WBRT and were randomized to receive placebo or memantine (20 mg/d), within 3 days of initiating radiotherapy for 24 weeks. Serial standardized tests of cognitive function were performed. Of 554 patients who were accrued, 508 were eligible. Grade 3–4 events were reported for 28% of patients on each of the 2 treatment arms. Grade 3–4 events that were attributable to treatment were reported for 14% of patients on each treatment arm, with the most common side effects being fatigue, alopecia, nausea, and headache, but there were no statistically significant differences between the treatment arms. No grade 5 treatment-related events were reported. There was less decline in delayed recall in the memantine arm at 24 weeks (P = .059). The memantine arm had significantly longer time to cognitive decline (hazard ratio 0.78, 95% confidence interval 0.62 – 0.99, P = .01); the probability of cognitive function failure at 24 weeks was 53.8% in the memantine arm and 64.9% in the placebo arm. Superior results were seen in the memantine arm for executive function at 8 (P = .008) and 16 weeks (P = .0041) and for processing speed (P = .0137) and delayed recognition (P = .0149) at 24 weeks. Memantine was well tolerated and had a toxicity profile very similar to placebo. Although there was less decline in the primary endpoint of delayed recall at 24 weeks, this lacked statistical significance possibly due to significant patient loss. Overall, patients treated with memantine had better cognitive function over time; specifically, memantine delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed in patients receiving WBRT.
3.1.7 **Pharmacokinetic Studies**

*Human Pharmacokinetics:*
Peak Concentration at target dose 22.08 nanogram (ng) /mL ± 5.07 ng/ml and was found to rise in subjects with renal impairment. Time to Peak Concentration is 3 to 7 hours and was found to increase in subjects with renal impairment. Area Under the Curve 1941 nanograms (ng) hour/mL. The mean AUC increased in 8 subjects with mild renal impairment (mean creatinine clearance, CrCl, 60.9 milliliters (mL) per minute ± 7.9), 8 subjects with moderate (mean CrCl, 41.6 mL per minute ± 5), and 7 subjects with severe (mean CrCl, 20.1 mL per minute ± 5.7) renal impairment, respectively, compared to healthy subjects (mean CrCl, 93.5 mL per minute ±13.4) following the oral administration of 10 mg twice daily of memantine HCl. In healthy subjects (n=8) the AUC (0-12) was 954 nanograms (ng) hour/mL ± 199 ng hour/mL, in renally impaired individuals, the AUC (0-12) increased to 1083 ng hour/mL ± 297 ng hour/mL (mild), 1504 ng hour/mL ± 327 ng hour/mL (moderate), and 990 ng hour/mL ± 267 ng hour/mL (severe).

3.1.8 **Pharmaceutical Data**

*Supplied:*
Memantine is commercially available as 5 mg and 10 mg tablets. Please refer to the product monograph for additional information.

*Stability/Storage:*
Memantine tablets should be stored in a dry place at room temperature between 15-30°C (59-86°F).

*Route of Administration:*
Memantine is administered orally.

3.1.9 **Expected Adverse Events**

Memantine is well-tolerated with incidence of adverse effects in clinical trials being similar to placebo. Most commonly reported adverse events include dizziness (7%), headache (6%), constipation (5%), hypertension (4%), coughing (4%), pain (3%), and dyspnea (2%). Symptoms of pharmacologic toxicity appear to be dose dependent and include hallucinations, anxiety / nervousness, changes in behavior, tremor, confusion, and other central nervous system symptoms. Other reactions to monitor include akathisia, restlessness, increased motor activity, insomnia, fatigue, loss of appetite, vomiting, sleep disturbances, and changes in frequency of urination. Uncommon side effects include infection, allergic reaction/hypersensitivity/skin allergies, abnormal gait, heart failure, thrombus/thrombosis/embolism, seizure, organ failure, and changes in vision.

3.1.10 **Drug Interactions**

The combined use of memantine with other compounds that are chemically related to NMDA antagonists may cause more frequent and pronounced adverse drug reactions, and therefore these should be avoided. These include amantadine, ketamine, and dextromethorphan (DM).

Concomitant use of drugs that make the urine alkaline may increase plasma concentration of memantine with a possible increase in adverse events. Examples of drugs that increase urine pH include: acetazolamide, dichlorphenamide, methazolamide, sodium bicarbonate.
Co-administration of drugs that use the same renal cationic system may result in altered plasma levels of memantine and the co-administered drug. Examples of drugs that use the same renal cationic system include: cimetidine, ranitidine, hydrochlorothiazide, nicotine, quinidine. If possible, patients should avoid use of medications that use the same renal cationic system and/or increase urine pH.

Other drugs that may interact with memantine include procainamide, quinine, anticholinergics, L-dopa and dopaminergic agonists (drugs such as bromocriptine, ropinirole, pramipexole), and anticoagulant blood thinner medications taken by mouth.

If the medications must be used, patients should be monitored for signs of memantine toxicity including lethargy, hallucinations, tremor, agitation and insomnia.

3.2 Stereotactic Radiosurgery (SRS)

Stereotactic radiosurgery utilizes immobilization, detailed imaging methods and computerized 3 dimensional treatment planning systems to deliver high doses of focal radiation in a highly precise manner in a single fraction or up to 5 fractions. The device types generally used include multiple source cobalt units (Gamma Knife), non-isocentric robotic linear accelerators (Cyberknife), and isocentric Linear Accelerator (Linac) based systems.

The Gamma Knife is based on multiple cobalt sources arranged in a semi-spherical arrangement.

Each cobalt source emits gamma ray irradiation, and the average beam energy is 1.25 MeV. A sophisticated collimation system allows for the convergence of multiple beams of irradiation to a focus (isocenter) within the treatment volume, effectively delivering a highly focused “shot” of radiation. Several shots of radiation directed to the target volume combine in the delivery of the prescribed treatment dose. Gamma Knife technology has been based on using an invasive head frame for immobilization; however, the Gamma Knife now has a dedicated frameless system that allows for frameless image-guided SRS delivery.

The Cyberknife consists of a miniaturized linac mounted onto a robotic arm. There is an integrated image-guidance system. The robot moves the linac around the patient and the 6MV beam is collimated using different sized circular collimators or even an MLC system specific to Cyberknife technology. Due to the integrated image-guidance system and near-real time feedback of the patient’s cranium position, this system allows for frameless SRS.

Linac-based systems are the most common technology delivering SRS. Essentially, a high-energy beam is shaped using different sized circular cones or multileaf collimators to conform to the target volume. Linac-based SRS was historically based on using an invasive stereotactic head frame, however, non-invasive frameless head immobilizations systems are now available and in use to deliver frameless image-guided SRS. Historically, a separate treatment isocenter has been used for each metastasis treated. This has made Linac treatment of multiple metastases cumbersome. With the use of robotic six-dimensional patient positioning, sophisticated image-guidance and appropriate quality assurance, it is now possible to treat multiple metastases using a single isocenter and volumetric intensity-modulated radiotherapy.
Regardless of the delivery system, standards for SRS have to be followed according to AAPM guidelines. Commissioning of the various SRS delivery systems is well defined in these guidelines. The biological effect should be equivalent regardless of the technology such that radiation induces DNA damage leading to cell kill. Although all systems will be able to deliver the prescribed dose to the periphery of the metastases, the dose distribution within the metastases, in the adjacent brain and the rest of the cranium may differ. The clinical impact of these differences is not well known.

3.3 Adverse Events for SRS

Acute toxicity may result from radiation-induced edema and may require dexamethasone use. Acute edema may manifest through headaches, nausea, vomiting, or a worsening focal neurological deficit. Rarely are more serious side effects may be observed which can consist of obstructive hydrocephalus, a new acute neurological deficit or seizure (1%). The most significant late side effect consists of radiation necrosis. Asymptomatic radiographic necrosis can occur in 10-20% of patients with symptomatic radiation necrosis occurring in <10% of patients. Radiation necrosis represents an inflammatory reaction of the irradiated tissue and can mimic tumour progression. Typically, the patient experiences symptoms and dexamethasone initiated although hyperbaric oxygen therapy or bevacizumab may be considered. Rarely, if a major neurologic deficit is present, or there is a doubt as to the diagnosis, then surgery may be required. Typically radiation necrosis resolves with conservative treatment and confirmatory MRI scans show stability or regression as opposed to progression. With well-defined dose limits, damage to other sensitive tissues in the brain such as the optic structures and brainstem is extremely rare. Precise pre-treatment planning is necessary to avoid damage to these organs at risk, and the dose limits proposed in this trial represents well defined standards for safe practice.

If using a head frame, other side effects associated with SRS include pain (temporary pain from frame placement) and possibly bleeding, allergic reaction or infection. Radiosurgery may also be associated with focal alopecia, decreased brain function, damage to brain tissue and vasculature which may require surgery, thrombosis/thrombus/embolism, stroke or changes in vision. Development of new cancers is a theoretical risk which may not be relevant to the patient population of this trial.

3.4 Hippocampal-Avoidant Whole Brain Radiation Therapy (HA-WBRT)

HA-WBRT is a type of external radiation therapy where x-ray beams are delivered to the whole brain over a period of weeks. The target volume consists of the entire brain from frontal lobes to occiput and vertex to foramen magnum. All patients will receive single daily fractions using intensity modulated radiotherapy, which will be required to conformally avoid the hippocampus while maintaining dose homogeneity. Correction for tissue heterogeneity will be mandated.

3.5 Expected Adverse Events for HA-WBRT

Cranial irradiation is generally acutely well tolerated.

Acute adverse events associated with HA-WBRT include alopecia, skin changes (rash, pruritis, dry skin), fatigue, nausea, cognitive disturbances, dry mouth, taste changes, headache, temporary ear canal redness, plugging or drainage, and drowsiness.
Delayed adverse events associated with HA-WBRT include cognitive disturbances such as memory loss, decreased brain function and motor function, changes to vision including cataracts, fatigue/drowsiness, taste changes, thrombosis/thrombus/embolism, stroke, and a theoretical risk of developing new cancers.
4.0 STUDY POPULATION

This is an international multi-centre, open-label, randomized phase III trial comparing stereotactic radiosurgery (SRS) to hippocampal-avoidant whole brain radiotherapy (HA-WBRT) plus memantine in patients with 5 or more brain metastases.

A two step registration/randomization process will be used for this trial.

4.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of registration or randomization. Questions about eligibility criteria should be addressed prior to enrolment.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfil all of the following criteria to be eligible for admission to the study:

4.1.1 Patients must have 5 or more brain metastases as counted on a T1 contrast enhanced MRI obtained ≤ 30 days from randomization.

4.1.2 Patients must have a pathological diagnosis (cytological or histological) of a non-hematopoietic malignancy.

4.1.3 The largest brain metastasis must measure <2.5 cm in maximal diameter.

The total tumour volume must be 30 cm³ or less. Lesion volume will be approximated by measuring the lesion’s three perpendicular diameters on contrast-enhanced, T1-weighted MRI and the product of those diameters will be divided by 2 to estimate the lesion volume (e.g. xyz/2). Alternatively, direct volumetric measurements via slice by slice contouring on a treatment planning software package can be used to calculate the total tumour volume.

4.1.4 Centre must either have the ability to treat patients with either a Gamma Knife, Cyberknife, or a linear accelerator-based radiosurgery system, or access to a centre at which the trial is open which can treat with using one of these systems.

4.1.5 Patient must be ≥ 18 years of age.

4.1.6 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires in either English or French either alone or with assistance. The baseline assessment must be completed within required timelines, prior to randomization.

Patient must also be able and willing to complete the neurocognitive testing without assistance from family and companions. Because this is one of the primary goals of this study, patients must be fluent in English or French, and fully testable in one of those languages.

A patient that is able but unwilling to complete the questionnaires will be considered ineligible.
4.1.7 ECOG performance status 0, 1, or 2.

4.1.8 Creatinine clearance must be $\geq 30$ ml/min within 28 days prior to registration.

4.1.9 The Neurocognitive Testing examiner must have credentialing confirming completion of the neurocognitive testing training.

4.1.10 The enrolling facility is credentialed by IROC to perform SRS and HA-WBRT - or have access to a centre where these treatments are credentialed and the study is open. The treating centre must have completed stereotactic radiosurgery credentialing of the specific system(s) to be used in study patients. The treating centre must have completed IMRT credentialing of the specific IMRT system(s) to be used in study patients for the purposes of HA-WBRT.

4.1.11 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrolment in the trial to document their willingness to participate.

A similar process must be followed for sites outside of Canada as per their respective cooperative group’s procedures.

4.1.12 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

4.1.13 In accordance with CCTG policy, protocol treatment is to begin within 14 days of patient enrolment.

4.1.14 Women/men of childbearing potential must have agreed to use a highly effective contraceptive method. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 5.0); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin is high and partner is vasectomized, it may be associated with tumour production of hCG, as seen with some cancers. Patient will be considered eligible if an ultrasound is negative for pregnancy.

4.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Pregnant or nursing women.

4.2.2 Men or women of childbearing potential who are unwilling to employ adequate contraception.
4.2.3 Inability to complete a brain MRI.

4.2.4 Known allergy to gadolinium.

4.2.5 Prior cranial radiation therapy.

4.2.6 Planned cytotoxic chemotherapy within 48 hours prior or after the SRS or HA-WBRT.

4.2.7 Primary germ cell tumour, small cell carcinoma, or lymphoma.

4.2.8 Widespread definitive leptomeningeal metastasis. This includes cranial nerve palsy, leptomeningeal carcinomatosis, ependymal involvement, cranial nerve involvement on imaging, suspicious linear meningeal enhancement, or cerebrospinal fluid (CSF) positive for tumour cells.

4.2.9 A brain metastasis that is located ≤ 5 mm of the optic chiasm or either optic nerve.

4.2.10 Surgical resection of a brain metastasis (stereotactic biopsies will be allowed).

4.2.11 Prior allergic reaction to memantine, or hypersensitivity to any excipients of memantine.

4.2.12 Current alcohol or drug abuse.

4.2.13 Current use of NMDA antagonists, such as amantadine, ketamine, or dextromethorphan.

4.2.14 Diagnosis of chronic liver disease/cirrhosis of the liver (e.g. Child-Pugh class B or C).

4.2.15 Clinically significant untreated or uncontrolled cardiovascular conditions, and/or symptomatic cardiac dysfunction (i.e. unstable angina, congestive heart failure, myocardial infarction within the previous year, cardiac ventricular arrhythmias requiring medication, history of 2nd or 3rd degree atrioventricular conduction defects, uncontrolled hypertension).

4.2.16 Current active or uncontrolled urinary tract infections (UTI).

4.2.17 History of epilepsy or seizures, and not currently taking anti-epileptic medication.

4.2.18 Any other serious intercurrent illness or medical condition judged by the local investigator to compromise the patients safety, preclude safe administration of the planned protocol treatment, or would not permit the patient to be managed according to the protocol guidelines.

4.2.19 Patients with architectural distortion of lateral ventricular systems which, in the opinion of the local investigator, makes hippocampal delineation challenging.
5.0 PATIENT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

All patients entered on study must be evaluated according to the schedule outlined below with documentation submitted according to the schedule in Appendix III.

<table>
<thead>
<tr>
<th>Required Investigations</th>
<th>Pre-study (within 14 days prior to randomization)</th>
<th>End of Protocol Treatment</th>
<th>After Protocol Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 8</td>
<td>Month 4</td>
<td>Month 6</td>
</tr>
<tr>
<td>History and Physical Exam</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Including: Height, Weight, Performance Status, Handedness</td>
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<td>X</td>
<td></td>
</tr>
<tr>
<td>Disease History, Prior Therapy</td>
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<td></td>
</tr>
<tr>
<td>Concurrent Illness and Concomitant Medications</td>
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<tr>
<td>Clinical tumour measurements (if applicable)</td>
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</tr>
<tr>
<td>Ophthalmology Exam</td>
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</tr>
<tr>
<td>Biochemistry* (within 28 days of randomization)</td>
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<td></td>
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<tr>
<td>Creatinine, Creatinine Clearance, BUN</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Radiology†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MRI of the Brain</td>
<td>X</td>
<td>(within 30 days prior to randomization)</td>
<td>X</td>
</tr>
<tr>
<td>Other Investigations**</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Neurocognitive Assessment</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (if applicable)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlative Studies***</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Whole Blood for cfDNA quantification and extraction</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Whole Blood, Plasma, Serum for circulating biomarkers</td>
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<tr>
<td>Whole blood, Plasma, Serum for banking (optional)</td>
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</tr>
<tr>
<td>Urine</td>
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</tr>
<tr>
<td>Adverse Events</td>
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<tr>
<td>Adverse Event Assessment</td>
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</tr>
<tr>
<td>Quality of Life****</td>
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</tr>
<tr>
<td>EORTC QLQ-C30 + BN20</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Health Economics</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Health Utilities Index (EQ-5D-5L)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Resource Utilization Assessment (CNS directed utilization only)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*footnotes on next page ...
5.1 Follow-up for Ineligible Patients

The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report plus an annual short follow up form. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

5.2 Follow-up After Progression in the Brain or Progression of Systemic Disease

In the event of progressive disease (PD) in the brain or progression of systemic disease, a Relapse/Progression Folder should be completed. Patients will continue to be followed as per the test schedule in Section 5 for survival status, new cancer treatments, correlative studies, adverse events, and health economic evaluations.

Quality of life and neurocognitive assessment information should be reported at the time of progression, but follow-up should also continue post progression as per Section 5 of the protocol.

Radiological investigation is no longer required after objective progression has been documented, and will be at the discretion of the investigator.

For patients who transfer to palliative care post progression and are no longer able to attend clinic for protocol specified visits or complete the protocol specified investigations, short follow up reports may be used for follow-up reporting. These short follow up reports should be completed at the same schedule as outlined in Section 5 of the protocol for regular follow up reporting.
ENTRY/ENROLLMENT PROCEDURES

6.1 Investigator Registration Procedures

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/iamp). 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).

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

<table>
<thead>
<tr>
<th>Documentation Required</th>
<th>IVR</th>
<th>NPIVR</th>
<th>AP</th>
<th>A</th>
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<tr>
<td>FDA Form 1572</td>
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<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial Disclosure Form</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>NCI Biosketch (education, training, employment, license, and certification)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>GCP training</td>
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<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Agent Shipment Form (if applicable)</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV (optional)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

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 Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:
• Addition to a site roster;
• Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
• Act as the site-protocol Principle Investigator (PI) on the IRB approval; and
• Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL) (NA for this trial).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm.

For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

6.2 Local Activation Process

6.2.1 US Local Activation Procedures

For Canadian activation procedures, please see Section 6.2.2

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

IRB Approval:

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

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

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

• Local IRB documentation,
• IRB-signed CTSU IRB Certification Form, and/or
In addition, the Site-Protocol PI (i.e., the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status,
- Active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization’s roster,
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements:

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

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

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.

Downloading Site Registration Documents:

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

- Log in to the CTSU members’ website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on Protocols in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select CCTG, and protocol number CCTG-CE.7
• Click on Documents, Protocol Related Documents, and use the Document Type filter and select Site Registration to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Protocol Specific Requirements For Site Registration:

• 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)

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

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

• Neurocognitive certification

• Radiation Therapy (RT) Credentialing

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

Neurocognitive Certification:

Sites will require neurocognitive certification as part of their local activation process. Patients may not be enrolled until at least one member of the site study team has received certification to perform neurocognitive testing.

This study requires that the member(s) of the study staff (i.e. physician, nurse, CRA, etc.) who will administer the neurocognitive testing to patients be credentialed by Dr. Alissa Butts, Medical College of Wisconsin. Each individual member of the study staff who will be administering the neurocognitive testing must be credentialed.

Details of the local activation process are available by contacting CCTG, or by visiting the trial website.

RT Credentialing and RTFI Form Submission to CTSU:

In order to utilize Stereotactic Radiosurgery (SRS) or Hippocampal-Avoidant Whole Brain Radiotherapy (HA-WBRT) on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements are available on the IROC Houston’s website at http://irochouston.mdanderson.org under “Credentialing”. To determine if these requirements have already been met by your institution, select “Credentialing Status Inquiry.”
Please refer to Section 7.5 for details of RT credentialing.

**Submitting Regulatory Documents:**

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

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

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

**Checking Your Site’s Registration Status:**

Site’s registration status may be verified on the CTSU website.

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

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

### 6.2.2 Canadian Local Activation Procedures

*For US activation procedures, please see Section 6.2.1*

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 REB approval for this protocol, and submit approval and supporting documentation to CCTG before they can be approved to enroll patients. Once site credentialing is approved, CCTG will notify CTSU directly.

See trial website for additional details.
In addition, the Site-Protocol PI (i.e., the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status,
- Active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization’s roster,
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements:

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

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

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

- Log in to the CTSU members’ website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on Protocols in the upper left of the screen
  o Enter the protocol number in the search field at the top of the protocol tree, or
  o Click on the By Lead Organization folder to expand, then select CCTG, and protocol number CCTG-CE.7
- Click on Documents, Protocol Related Documents, and use the Document Type filter and select Site Registration to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)
**Protocol Specific Requirements For Site Registration:**

- REB approval (see trial website for details)
- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members’ website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.
- Neurocognitive certification
- Radiation Therapy (RT) Credentialing

Additional details of local activation requirements will be available on the CE.7 trial website.

**Neurocognitive Certification:**

Sites will require neurocognitive certification as part of their local activation process. Patients may not be enrolled until at least one member of the site study team has received certification to perform neurocognitive testing.

This study requires that the member(s) of the study staff (i.e. physician, nurse, CRA, etc.) who will administer the neurocognitive testing to patients be credentialed by Dr. Alissa Butts, Medical College of Wisconsin. *Each individual member of the study staff* who will be administering the neurocognitive testing must be credentialed.

Details of the local activation process are available by contacting CCTG, or by visiting the trial website.

**RT Credentialing and RTFI Form Submission to CTSU:**

In order to utilize Stereotactic Radiosurgery (SRS) or Hippocampal-Avoidant Whole Brain Radiotherapy (HA-WBRT) on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements are available on the IROC Houston’s website at http://irochouston.mdanderson.org under “Credentialing”. To determine if these requirements have already been met by your institution, select “Credentialing Status Inquiry.”

Please refer to Section 7.5 for details of RT credentialing.
Submitting Regulatory Documents:

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

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

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

Checking Your Site’s Registration Status:

Site’s registration status may be verified on the CTSU website.

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

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

6.3 Enrollment Procedures

There will be two steps for enrollment on this study, a screening and an enrollment step. Both will be provided electronically. Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN).

Step 1 - Registration

All consenting patients who are believed to be eligible will be registered using the OPEN system. An abbreviated eligibility checklist will be used for this purpose. After registration, neurocognitive assessments, quality of life questionnaires, and health economics assessments may be administered.

Step 2 - Randomization

Randomization will be provided electronically, using the OPEN system. Patients must be randomized prior to the initiation of treatment, and after baseline assessments are completed.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG. The serial number will be assigned after registration for screening and will remain the same following enrollment.
The following information will be required at time of screening and enrollment:

- trial code (CCTG CE.7);
- patient's initials (may be coded);
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed;
- tissue banking/optional consent version date;
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values;
- height and weight;
- stratification factors.

6.3.1 **OPEN**

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

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site’s IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

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

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

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

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.

6.3.3 **General Guidelines**

At the time of enrollment, all data reported within the Patient Enrollment folder must be accurate, complete and verifiable against source documentation. CCTG should be contacted for assistance, if there are questions about patient eligibility or data entry in the OPEN system. Under no circumstances should inaccurate data be entered in order to permit enrollment.

Note: The validity of results of the trial depends on the authenticity of and the followup of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient’s data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting enrollment.

All enrolled patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible patients are outlined in Section 5.1.

All subsequent data entry tasks will be done through a web-based, password-operated Electronic Data Capture (EDC) system. Data must be submitted electronically using Medidata Rave® at the following url: https://login.imedidata.com/selectlogin.

- If prompted, select the ‘CTEP-IAM IdP’ link.
- Enter your valid and active CTEP-IAM User ID and password. This is the same account used for the CTSU members website and OPEN.

You may also access Rave® via the trial website. If sites experience difficulties accessing the system and/or enrolling patients please contact the help desk or the HN.11 Study Coordinator.

6.4 **Stratification**

Subjects will be stratified by:

- DS-GPA predicted median overall survival (< 6 months vs. ≥ 6 months);
- Use of targeted or immunotherapy within 4 weeks of original diagnosis of brain metastases, or planned for within 4 weeks of radiation therapy (yes or no);
- Histology (radio-resistant* vs. other).
- Metastasis within 5 mm of one hippocampus (yes or no)

* Radio-resistant is defined as brain metastases from a sarcoma, melanoma, or renal cell carcinoma histology.
6.5 **Inclusion of Women and Minorities**

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

Based on prior studies involving similar patient populations, estimated sizes of racial and gender subsets for patients randomized to this study are shown in the following table:

<table>
<thead>
<tr>
<th>Racial Categories</th>
<th>Ethnic Categories</th>
<th>Not Hispanic or Latino</th>
<th>Hispanic or Latino</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>American Indian/ Alaska Native</td>
<td></td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td></td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Black or African American</td>
<td></td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>68</td>
<td>103</td>
<td>4</td>
</tr>
<tr>
<td>More Than One Race</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>77</td>
<td>115</td>
<td>6</td>
</tr>
</tbody>
</table>
7.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 14 days of patient randomization.

Memantine will ideally start the same day as HA-WBRT and must start no later than before the fourth HA-WBRT treatment. If a patient is enrolled on study, and then are unable to acquire memantine or are non-compliant with the use of memantine, they should remain on study and proceed with protocol assigned therapy.

7.1 Radiation Treatment Plan

<table>
<thead>
<tr>
<th>Arm</th>
<th>Agent(s)</th>
<th>Dose</th>
<th>Duration</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HA-WBRT + memantine</td>
<td>30 Gy</td>
<td>10 fractions</td>
<td>Within 14 days of randomization</td>
</tr>
<tr>
<td>2</td>
<td>SRS</td>
<td>18-20 or 22 Gy</td>
<td>1 fraction</td>
<td>Within 14 days of randomization</td>
</tr>
</tbody>
</table>

7.1.1 Premedication

Premedication for HA-WBRT or SRS may be administered as per institutional guidelines.

Patients may be given oral or intravenous corticosteroids at the time of HA-WBRT or SRS, but this is not required and is at the discretion of the treating physician.

Patients must be suitable candidates for serial MRI imaging on study. If claustrophobic, then sedatives may be given as per institutional standards for the MRI and SRS procedure.

7.1.2 Patient Compliance

Treatment details will be recorded on the case report form, and protocol adherence will be verified through radiotherapy quality assurance (RTQA).

7.1.3 Patient Evaluation

Prior to treatment and after informed consent is obtained, baseline assessments must have been completed. Before treatment can start, baseline QoL, neurocognitive assessments, and relevant correlative study samples must be completed/obtained.

Additional pre-treatment evaluations and assessments may be done as per institutional standards.

Performance of SRS or HA-WBRT at a Site Other than the Registering Site:
Only participating sites that have been credentialed for SRS or HA-WBRT may enroll and treat patients.

The radiosurgery or HA-WBRT can be delivered at a different site than the site enrolling the patient as long as the site is also participating on the study, the treatment guidelines are followed and the site delivering the SRS or HA-WBRT has been credentialed by the IROC Quality Assurance Centers, and there is a patient sharing agreement between the two centres.
The Qualified Investigator from the enrolling site is ultimately responsible for all aspects of the clinical trial and should have an established relationship with the institution delivering treatment, such that they are willing to take responsibility for accurately and timely provision of evidence of treatment. This includes provision of all relevant data and supporting documentation for the purposes of data entry in the EDC system and upload for case review of treatment planning and delivery.

*Note:* Please inform IROC Quality Assurance Center, CCTG, NRG Oncology, and Alliance that your site will register the patient and perform SRS or HA-WBRT at another site; please include the sites’ names and CTEP site codes. Without this information, CTSU may delay the registration of the patient as it would have no SRS credentialing on file for the registering site.

### 7.1.4 Neuroimaging

Anatomic MR images will be acquired at pre-registration (within 30 days prior to randomization) and at 8 weeks, 4 months, 6 months, 9 months, 12 months, 16 months and 24 months then annually after protocol therapy.

A planning MRI must also be acquired within 14 days prior to the start of treatment. The diagnostic (baseline) MRI may also be used for planning if it was performed within this timeline.

**Planning MRI for HA-WBRT and SRS:**
Patients **must** have a post gadolinium contrast-enhanced three-dimensional inversion-recovery gradient-recalled echo sequence (IR-GRE). The IR-GRE sequence is equivalent to MPRAGE = magnetization prepared rapid gradient-echo and the inversion recovery spoiled gradient-echo (IR-SPGR or Fast SPGR), 3D turbo field echo (TFE), or 3D fast field echo (3D Fast FE). To yield acceptable image quality, the gadolinium contrast-enhanced three-dimensional IR-GRE scan should use the smallest possible axial slice thickness not exceeding 1 mm. When CT will be used for SRS or HA-WBRT treatment planning, immobilization devices used for CT simulation and radiation therapy are not required when obtaining MRI imaging sequences required on study.

**HA-WBRT Simulation Imaging:**
When CT is used for planning, a treatment planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2.5 mm will be required. The planning CT must be acquired with the patient in the same position and immobilization device as for treatment.

Note that a CT simulation alone is not adequate for planning purposes. It must accompany a planning MRI.

When both CT and MRI are used for planning, the baseline (pre-treatment) MRI and treatment planning CT should be fused for hippocampal contouring.
In lieu of CT-based planning, an MRI in treatment position with an MRI-derived synthetic CT may be used for planning of HA-WBRT. A site that chooses to use MR-based planning must obtain both an MRI-derived synthetic CT as well as a conventional CT simulation on the first patient that they enroll. Both the MRI and the CT must be acquired with the patient in the same position and immobilization device as for treatment. HA-WBRT IMRT plans using both the MR-based planning system as well as the conventional CT-based planning system must be performed and submitted for external pre-treatment case review. If the MR-based plan is consistent the CT-based plan and consistent with protocol-defined treatment planning criteria, then the patient may proceed with treatment, and the site is permitted to use MR-based planning for subsequent patients treated with HA-WBRT on this trial. Please consult the RTQA Manual for additional information.

When both CT and MRI are used for treatment planning, the MRI must not be performed more than 14 days prior to the CT simulation (the CT simulation must have been completed within 14 days of treatment start).

**SRS Simulation Imaging:**
When CT is used for planning, a treatment planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2.5 mm will be required - the used of IV contrast is recommended. The planning CT must be acquired with the patient in the same position and immobilization device as for treatment.

Note that a CT simulation alone is not adequate for planning purposes. It must accompany a planning MRI.

Simulation may also be performed using only MRI performed with the patient immobilized as for radiosurgery. When both CT and MRI are used for planning, a planning MRI and treatment planning CT are co-registered for contouring. When both CT and MRI are used, immobilization devices used for CT simulation and radiosurgery is not required when obtaining MRI imaging sequences required on study.

When both CT and MRI are used for treatment planning, the MRI must not be performed more than 14 days prior to the CT simulation (the CT simulation must have been completed within 14 days of treatment start).

### 7.2 Equipment and Treatment Delivery: Hippocampal-Avoidant Whole Brain Radiation Therapy (HA-WBRT) Guidelines

HA-WBRT for patients on this protocol must be performed at IROC credentialed facilities. All patients receiving HA-WBRT will have all metastases treated in 10 fractions.

#### 7.2.1 Equipment

**Modality:**
This protocol requires photon treatment using intensity-modulated radiation therapy (IMRT) for delivery of WBRT with hippocampal avoidance. All sites must be credentialed for IMRT. Fixed-gantry IMRT, helical tomotherapy, or VMAT may be used.

**Calibration:**
All participating sites must be credentialed for IMRT. The calibration of therapy machines to deliver HA-WBRT used in this study shall be verified by the IROC Quality Assurance Center.
7.2.2 **Treatment Delivery**

**Target Volume Definition:**
The gross tumor volume (GTV) includes metastases visible as contrast-enhanced lesions on the T1-contrast enhanced MRI. The GTV needs only to be segmented for lesions within 5 mm of the hippocampi. A 5 mm expansion of the GTV will be combined with the whole-brain parenchyma to the foramen magnum to form the clinical target volume (CTV). The planning target volume (PTV) excludes the hippocampal avoidance region but includes the GTV and associated 5mm margin. No set-up margin is added.

**Dose Uniformity:**
See table below.

**Treatment Interruptions:**
No corrections shall be made for treatment interruptions.

7.2.3 **Target Dose**

**Prescription Point:**
The IMRT plan should be normalized such that 95% of the PT_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 acceptable. The following compliance criteria 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.

These structures are required and 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.

**Normal Structure Constraints and Compliance Criteria:**

<table>
<thead>
<tr>
<th>Name of Structure</th>
<th>Dosimetric Parameter</th>
<th>Per Protocol</th>
<th>Variation Acceptable</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV_3000</td>
<td>D2% (Gy)</td>
<td>≤ 37.5</td>
<td>37.5 to 40</td>
<td>Dose to hottest 2% of PTV_3000</td>
</tr>
<tr>
<td></td>
<td>D98% (Gy)</td>
<td>≥ 25</td>
<td>22.5 to 25</td>
<td>Dose to 98% of PTV_3000</td>
</tr>
<tr>
<td></td>
<td>V30(Gy) (%)</td>
<td>≥ 95</td>
<td>90 to 95</td>
<td>Volume receiving prescription dose of 30 Gy</td>
</tr>
<tr>
<td>GTV_3000</td>
<td>D100% (Gy)</td>
<td>≥ 28.5</td>
<td>27 to 28.5</td>
<td>Dose to 100% of visible metastases within 5 mm of the hippocampi</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>D100% (Gy)</td>
<td>≤ 9</td>
<td>9 - 10</td>
<td>Dose to 100% of hippocampus</td>
</tr>
<tr>
<td></td>
<td>Dmax (Gy)</td>
<td>≤ 16</td>
<td>16 – 17*</td>
<td>Dose to hottest 0.03cc volume of hippocampus</td>
</tr>
<tr>
<td>OpticNerve_L</td>
<td>Dmax (Gy)</td>
<td>≤ 30</td>
<td>30 - 37.5</td>
<td>Dose to hottest 0.03cc volume of optic nerve</td>
</tr>
<tr>
<td>OpticNerve_R</td>
<td>Dmax (Gy)</td>
<td>≤ 30</td>
<td>30 - 37.5</td>
<td>Dose to hottest 0.03cc volume of optic nerve</td>
</tr>
<tr>
<td>OpticChiasm</td>
<td>Dmax (Gy)</td>
<td>≤ 30</td>
<td>30 - 37.5</td>
<td>Dose to hottest 0.03cc volume of optic chiasm</td>
</tr>
</tbody>
</table>

* the maximum dose constraint will not apply to patients with metastases within 5mm of the hippocampi but efforts will be made meet the constraints to the regions of the hippocampi more than 5mm removed from the GTV
**Dose Definition:**
The absorbed dose is specified below in Gy to muscle or water.

**Tissue Heterogeneity:**
Corrections for tissue heterogeneity are required.

**Prescribed Dose and Fractionation:**
All patients receiving HA-WBRT plus memantine will receive single daily fractions of 3 Gy per fraction to 30 Gy. IMRT will be used for this purpose.

In the event that an OAR with higher priority than PTV cannot be constrained within limits, then $D_{98\%}$ and/or $V_{30\text{Gy}}$ for PTV should be lowered to an acceptable range to ensure that the OAR with higher priority does not exceed the acceptable limits. In cases where a GTV is defined, the dose to the GTV should not be reduced below 27 Gy to meet constraints on the Hippocampi but may be lowered to meet the other normal tissue constraints.

Primary dataset for dose calculation should be the treatment planning CT scan of the entire head region, or a synthetic CT of the entire head region. Dose matrix grid size must be $\leq 3$mm in sagittal and coronal directions.

SRS boosts to metastases are not permitted after HA-WBRT.

### 7.2.4 Treatment Technique

**Patient Position:**
It is recommended that the patient be treated supine.

**Immobilization:**
A thermoplastic mask and head-holding device (headrest) that is transparent to x-rays must be used in order to ensure adequate immobilization during therapy, and to ensure reproducibility.

**Localization Imaging:**
For all forms of IMRT dose delivery, daily localization imaging is required. The localization imaging may be CT, x-ray or MRI.

### 7.2.5 Normal Tissue/Critical Structures and Margins

The treatment parameters should be modified to optimize the fit of the prescription volume to the target volume, while minimizing dose to critical structures. All organs at risk (OAR) listed below should be contoured on the planning CT, using fused MRI for guidance as described below.

These structures are required and 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.
**PROTOCOL ADMINISTRATIVE UPDATE #2: 2022-APR-01**  
**CCTG TRIAL:** CE.7

<table>
<thead>
<tr>
<th>Standard Name</th>
<th>Description</th>
<th>Description Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampi</td>
<td>Bilateral hippocampal contours</td>
<td>Bilateral hippocampal contours will be manually generated on the planning MRI or fused planning MRI/CT image set by the treating physician according to contouring instructions specified on: <a href="https://www.nrgoncology.org/ciro-brain">https://www.nrgoncology.org/ciro-brain</a></td>
</tr>
<tr>
<td>Hippocampi_05</td>
<td>Hippocampal avoidance region</td>
<td>Generated by three-dimensionally expanding the hippocampal contours by 5 mm and subtracting the GTV with an additional 5 mm margin.</td>
</tr>
<tr>
<td>Hippo_L</td>
<td>Left hippocampus</td>
<td>Bilateral hippocampal contours will be subdivided into left and right hippocampus</td>
</tr>
<tr>
<td>Hippo_R</td>
<td>Right hippocampus</td>
<td></td>
</tr>
<tr>
<td>Lens_L</td>
<td>Left lens</td>
<td>The lenses should be contoured on the image set used for dose calculation</td>
</tr>
<tr>
<td>Lens_R</td>
<td>Right lens</td>
<td></td>
</tr>
<tr>
<td>OpticNerve_L</td>
<td>Left optic nerve</td>
<td></td>
</tr>
<tr>
<td>OpticNerve_R</td>
<td>Right optic nerve</td>
<td></td>
</tr>
<tr>
<td>OpticChiasm</td>
<td>Optic chiasm</td>
<td>Located above the pituitary fossa, the optic chiasm includes both anterior and posterior limbs. It is best visualized on MRI sequencing, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion</td>
</tr>
</tbody>
</table>

### 7.3 Memantine

#### 7.3.1 Drug Administration

Memantine will ideally start the same day as WBRT and must start no later than before the fourth WBRT treatment. The target dose for memantine is 20 mg (10 mg divided twice daily). Dose will be escalated by 5 mg per week. Memantine should start at 5 mg, and then increased in 5 mg increments at the following schedule, depending on the patient’s response and tolerance:

<table>
<thead>
<tr>
<th>Timing</th>
<th>AM</th>
<th>PM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>1 x 5 mg tablet</td>
<td>None</td>
</tr>
<tr>
<td>Week 2</td>
<td>1 x 5 mg tablet</td>
<td>1 x 5 mg tablet</td>
</tr>
<tr>
<td>Week 3</td>
<td>1 x 10 mg tablet</td>
<td>1 x 5 mg tablet</td>
</tr>
<tr>
<td>Weeks 4 - 24</td>
<td>1 x 10 mg tablet</td>
<td>1 x 10 mg tablet</td>
</tr>
</tbody>
</table>

**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).

*Note: The extended release formulation is not currently available in Canada, and therefore this formulation of memantine should not be used in Canada.*

<table>
<thead>
<tr>
<th>Timing</th>
<th>Daily Dose Extended Release Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>7mg</td>
</tr>
<tr>
<td>Week 2</td>
<td>14mg</td>
</tr>
<tr>
<td>Week 3</td>
<td>21mg</td>
</tr>
<tr>
<td>Weeks 4 - 24</td>
<td>28mg</td>
</tr>
</tbody>
</table>
The tablets can be taken with or without food. They should be swallowed whole with some water. If a dose is missed, the patient should be instructed to take the next dose as scheduled. Doses should not be made up. The drug should be taken for a maximum of 24 weeks, regardless of disease status (if tolerated).

**Memantine Pill Diary:**
Prior to starting treatment, the patient should be provided with a pill diary, and instructed to record daily pill consumption. This diary should be retained on site, and should be used to assess patient compliance with memantine use.

### 7.3.2 Dose Modifications

Approximately 50% of memantine is metabolized by the liver, the remaining 50% is excreted unchanged by the renal system. A dosage reduction to 5 milligrams (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 criteria is for creatinine clearance ≥ 30 ml/min. In patients with moderate renal impairment (CrCl 30 to 49 mL/min), the daily dose should be 10 mg per day. If well tolerated after at least 7 days of treatment, and based on clinical response, the dose may be increased up to 20 mg/day according to the standard titration scheme. No dosage adjustment is needed in patients with mild renal impairment (CrCl greater than 50 to 80 mL/min).

Creatinine should be evaluated at each follow-up evaluation while taking memantine. Protocol treatment will be dose modified based on criteria outlined in the dose modification table.

<table>
<thead>
<tr>
<th>BUN (mg/dL)</th>
<th>*Creatinine Clearance (CrCl) (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50</td>
<td>5 mg by mouth twice daily</td>
</tr>
<tr>
<td>30-49</td>
<td>5 mg by mouth twice daily Recheck value weekly; If CrCl not &gt; 29 (mL/min) by 3 weeks, continue at reduced dose throughout protocol treatment</td>
</tr>
<tr>
<td>5-29</td>
<td>HOLD STUDY DRUG Recheck value weekly; If CrCl not &gt; 5 (mL/min) by 3 weeks, discontinue protocol treatment</td>
</tr>
</tbody>
</table>

| ≤ 20        | 10 mg by mouth twice daily            |
| > 20        | HOLD STUDY DRUG Recheck value in one week; If BUN not < 20 mg/dL 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)]

In the event of grade 3 or greater toxicity considered related to memantine, study drug should be held until recovery to grade 1 or baseline.

### 7.4 Equipment and Treatment Delivery: Stereotactic Radiosurgery (SRS) Guidelines

Radiosurgery for patients on this protocol can only be performed at IROC credentialed facilities.
All patients receiving SRS will have all metastases treated in a single fraction, though all lesions need not be treated on the same day. All lesions must be treated within 7 days of each other. Hypofractionation is not allowed.

7.4.1 Equipment

Modality:
Gamma knife or X-rays with nominal energy of 4 megavoltage (MV) or greater for accelerator-based treatments, including isocentric conical collimators, mini-multi-leaf (5 mm or less) technology or linear accelerators mounted on robotic arms.

Calibration:
The calibration of linear accelerators and Gamma Knife units used in this study shall be verified by the IROC Houston Quality Assurance Center.

7.4.2 Treatment Delivery

Target Volume Definitions:
The volumes shall be defined by a planning MRI brain scan, which should be performed within 14 days of SRS delivery. ICRU-50 and supplement (ICRU-62) nomenclature target volumes are defined as follows:

Gross Tumour Volume (GTV):
This is defined as the contrast enhancing tumour on T1 with contrast scans. Surrounding blood and edema will be excluded from the target volume. The metastases will be numbered and named GTV1, GTV2, GTV3 and so on from the most cranial axial image to the most caudal. When multiple tumour volumes appear on the same slice, they will be numbered front to back.

Clinical Target Volume (CTV):
No additional margin will be added from the GTV, thus the CTV will be equal to the GTV. As CTV is equal to GTV, no explicit CTV volumes need to be created.

Planning Target Volume (PTV):
It is expected that for most treatment delivery techniques, no additional margin will be added to the GTV. However, 1 mm isotropic margin can be added when non-invasive immobilization is used for multiple-isocenter SRS. The PTVs will be numbered in the same manner as the GTVs: PTV1, PTV2, PTV3 and so on. When non-invasive immobilization is used on linear accelerators for single-isocenter treatment of multiple targets, 1 mm margins should be used with 6D setup correction, whereas 2 mm margins can be used with 3D setup correction.

7.4.3 Target Dose

Prescription Specification:
The dose should be prescribed to the highest isodose line encompassing the contrast enhancing metastasis (GTV, or PTV if applicable), which can range from 50% to 90% of the maximum dose. No more than 0.03cm³ of each GTV shall receive less than the prescribed dose. No more than 1% of each PTV shall receive less than the prescribed dose.

Dose Definition:
Dose is specified in Gray (Gy) to muscle or water.
**Prescription Dose:**
The total prescribed dose is determined by the CTV volume (excluding brainstem lesions):

<table>
<thead>
<tr>
<th>Brain Metastasis volume</th>
<th>Dose Prescribed to Tumour Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions &lt; 4 cc</td>
<td>22 Gy</td>
</tr>
<tr>
<td>Lesions 4-10 cc</td>
<td>18-20 Gy</td>
</tr>
</tbody>
</table>

Increasing or decreasing a prescribed dose by 2 Gy is allowed.

If *brainstem* lesions are detected on the high resolution SRS planning MRI, the following peripheral doses should be used:

<table>
<thead>
<tr>
<th>Brainstem Metastasis volume</th>
<th>Dose Prescribed to Tumour Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions 4-10 cc</td>
<td>14-16 Gy</td>
</tr>
<tr>
<td>Lesions 1- 4 cc</td>
<td>16-18 Gy</td>
</tr>
<tr>
<td>Lesions &lt; 1 cc</td>
<td>18-20 Gy</td>
</tr>
</tbody>
</table>

If organs at risk (OAR) constraints cannot be met, prescription dose can be reduced to the highest dose for which the constraints can be met with a prescription dose not below 14 Gy.

**Dose Conformity:**
The ratio of the prescription isodose volume to the target volume (CTV) should be between 1.0 and 2.0. It is understood that this ratio may be difficult to achieve with some very small lesions. For lesions less than 5 mm in size, a ratio up to 3.0 is acceptable.

**More than 30cm³ Total Brain Metastases Volume Observed:**
If at the time of planning MRI or CT scan for SRS more than 30cm³ of brain metastases are noted, the patient should remain on study. Perform volumetric measurement of the brain metastases on the MRI used to determine eligibility and contact the senior investigator/study chairs for guidance.

**Less than 5 Metastases Observed:**
If at the time of planning MRI or CT scan for SRS less than 5 metastases are observed (either because there has been a complete response to systemic therapy or the planning MRI is interpreted differently than the pre-registration MRI), those metastases visible at the time of planning should be treated as per protocol and the patient should continue follow-up on the assigned treatment arm.

7.4.4 **Treatment Technique**

**Patient Position:**
Patients should be supine with their arms by their side.
Immobilization:
An immobilization/patient localization system is mandatory for this study. Both invasive (frame-based) and non-invasive immobilization are permitted. Image-guidance is required in cases of non-invasive immobilization — this may be: cone-beam CT, a diagnostic quality CT scanner positioned with known geometry in the treatment room, tomotherapy technology that uses a fan-beam imaging approach, optical surface monitoring, stereoscopic x-ray images or a combination of these modalities.

Localization Imaging/Simulation:
The volumes shall be defined by a planning MRI brain scan. The planning MRI shall be a contrast-enhanced three-dimensional inversion-recovery gradient-recalled echo sequence (IR-GRE) with 3D distortion correction. The voxel size should be 1 mm³ or smaller (1 x 1 x 1 mm). The field strength of the MRI shall be 1.5T or greater. If a planning CT scan is also used, the use of iodinated contrast is encouraged to verify the CT-MRI fusion and to permit appreciation of rapid growth of brain metastases between the planning MRI and the planning CT scan.

7.4.5 Normal Tissue/Critical Structures

The treatment parameters should be modified to optimize the fit of the prescription volume to the target volume while minimizing dose to critical structures. OAR include the optic chiasm, optic nerves, optic tracts, brainstem, hippocampi, eyes and lenses. These should be contoured for all patients.

The following normal tissue constraints will be followed on the SRS arm of the study:

- Total Brain: The V12 of the brain minus the summed volume of the GTVs will be limited to 30 cm³ (30cc). For adjacent lesions in which the V12 combine, a structure named V12_a,b,c… (where a, b, c… are the metastasis numbers of the adjacent metastases) should be contoured around the volume of contiguous V12. The maximum allowable contiguous V12 inside this structure, minus the summed volume of the adjacent GTVs, a, b, c…, will be 8.5 cc. If this volume is exceeded, the prescription doses to the adjacent metastases must be lowered until this constraint is met. The median brain dose should be less than 8 Gy.
- Optic structures: The maximum point dose to the optic chiasm or either optic nerve should be 10 Gy. The maximum point dose for the lenses should be 5Gy, and should be 8Gy for the eyes.
- Brainstem: No more than 1 cc of the brainstem minus GTV should receive 12 Gy or more.
- Hippocampi: There is no dose constraint for the hippocampi in SRS plans.

Gamma Knife centers will not be required to report median brain dose or hippocampi doses due to limitations of the GammaPlan software. Median skull contour will be collected as a surrogate to median brain dose. Brainstem and optic doses at Gamma Knife centers will be collected in cases where a metastasis is within 1 cm of the metastasis.

7.4.6 Dose Calculation and Reporting

Treatment Time:
The monitor units or time required to deliver the prescribed dose shall be calculated and submitted.
**Dose Uniformity:**
The maximum and minimum doses in the GTV (or PTV) shall be calculated and reported. These may be extracted from isodose distributions, calculated separately or derived from Dose Volume Histograms (DVHs).

**Conformity Index:**
The PITV, defined as the ratio of the prescription isodose volume to the target volume GTV (or PTV), shall be calculated and reported.

**Normal Tissue and Critical Organ Dose Points:**
Documentation of the highest point dose to the optic chiasm shall be submitted, as will the V12 of the brainstem.

**Isodose Distribution:**
Three-dimensional DICOM – RT data will be submitted with the contoured organ-at-risk and target structures, as well as the isodose distribution.

7.5 **Radiation Therapy Quality Assurance**

The Radiotherapy Quality Assurance process for sites delivering SRS and HA-WBRT includes:

- Credentialing for RT delivery prior to local activation at institutional level.
- Prospective local pre-treatment peer review of all SRS cases.
- Retrospective external post-treatment case review of all SRS cases.
- Prospective central pre-treatment case review of the first HA-WBRT case
- Retrospective central post-treatment case review of all HA-WBRT cases

Please consult the RTQA manual for additional details.

7.5.1 **RT-Specific Pre-Registration Requirements**

For detailed information on the specific requirements for this study, please refer to the table below and utilize the web link provided for detailed instructions. Specific credentialing components may require you to work with various IROC offices; however, the Houston office will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.
### RT Credentialing Requirements

<table>
<thead>
<tr>
<th>RT Credentialing Requirements</th>
<th>Treatment Modality</th>
<th>Key Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facility Questionnaire</td>
<td>SRS, HA-WBRT</td>
<td>The IROC electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ go to <a href="http://irochouston.mdanderson.org/questionnaires">http://irochouston.mdanderson.org/questionnaires</a>.</td>
</tr>
<tr>
<td>Credentialing Status Inquiry Form</td>
<td>SRS, HA-WBRT</td>
<td>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 (<a href="http://irochouston.mdanderson.org">http://irochouston.mdanderson.org</a>).</td>
</tr>
<tr>
<td>Phantom Irradiation</td>
<td>SRS, HA-WBRT</td>
<td>An IROC Houston anthropomorphic phantom must be successfully completed if the institution has not previously met this credentialing requirement. Flattening-filter-free (FFF) photon beam delivery, Cyberknife, and Gammaknife treatment delivery modalities must be credentialled individually and separately from standard c-arm linac beams. Instructions for requesting and irradiating the phantom are available on the IROC Houston website under credentialing (<a href="http://irochouston.mdanderson.org">http://irochouston.mdanderson.org</a>).</td>
</tr>
<tr>
<td>MRI QA</td>
<td>SRS, HA-WBRT</td>
<td>Documentation of MRI phantom geometric QA, or submission of both planning CT and MRI for a non-protocol (e.g. previous) patient, or for the first enrolled patient on study. See RTQA Manual for requirements.</td>
</tr>
<tr>
<td>Benchmark Testing</td>
<td>SRS, HA-WBRT</td>
<td>Benchmark cases are to be downloaded and completed by each institution before submission to IROC via TRIAD. Sites are to generate an IMRT plan for HA-WBRT and submit for review. <strong>Note:</strong> Before a benchmark can be submitted the site must have IRB Approval and SRS credentialing completed. See the Study guide for more details.</td>
</tr>
</tbody>
</table>

### Credentialing Issued to:

**Institution**: IROC Houston QA Center will notify the institution that all desired credentialing requirements have been met. It is the institution’s responsibility to forward this information to the CTSU Regulatory Office.

#### 7.5.2 RTQA of Individual Cases

- For individual initial SRS treatments and for SRS retreatments, the study requires local pre-treatment peer review of the treatment planning imaging by a radiologist or a second radiation oncologist or neurosurgeon co-investigator and of the radiation treatment plan by a second radiation oncologist or neurosurgeon co-investigator. Pre-treatment completion and prompt submission of the case report form documenting the local peer review is encouraged.

- For HA-WBRT, the study requires a pre-treatment case review for the first patient receiving HA-WBRT by each credentialed physician. The RTQA procedures are described in the RTQA Manual.

- Details are presented in Section 3.0 of the RTQA Manual.

- Submission of all baseline SRS and WBRT treatment planning DICOM-RT CTs and MRIs to the American College of Radiology (ACR) Transmission of Imaging and Data (TRIAD) system. Treatment plan data (DICOM structure, plan, and dose files) should also be uploaded.
• Retrospective external individual post-treatment case review for all patients receiving SRS and HA-WBRT will be performed. The RTQA procedures will be described in a Radiotherapy Quality Assurance Manual.

• Submission of all post-treatment brain MRIs to TRIAD.

• Submission of all radiation treatment planning DICOM-RT CTs and MRIs for SRS and HA-WBRT plans to TRIAD.

• Continuous monitoring of retreatments for brain metastases, with comparisons of retreatment plans to prior plans in order to determine how often they were required because of a geographic miss of brain metastases during an earlier course of SRS.

• Continuous monitoring of radionecrosis events to assess the safety of treating 5or more brain metastases.

Digital Radiation Therapy Data Submission Using Transfer of Images and Data (TRIAD) (Required for patients):

TRIAD is the American College of Radiology’s (ACR) image exchange application. TRIAD provides sites participating in 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:

• A valid CTEP-IAM account.

• Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.

• TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

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

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

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

7.6 Concomitant Therapy

7.6.1 Permitted

The following drugs should be used with caution, or not used at all while on protocol therapy:
Drugs that increase the pH of urine, and/or that use the same renal cationic system as memantine:
Concomitant use of drugs that make the urine alkaline may increase plasma concentration of memantine with a possible increase in adverse events. Examples of drugs that increase urine pH include: acetazolamide, dichlorphenamide, methazolamide, sodium bicarbonate.

Coadministration of drugs that use the same renal cationic system may result in altered plasma levels of memantine and the coadministered drug. Examples of drugs that use the same renal cationic system include: cimetidine, ranitidine, hydrochlorothiazide, nicotine, quinidine.

If possible, patients should avoid use of medications that use the same renal cationic system and/or increase urine pH.

Drugs that potentially interact with memantine:
Other drugs that may interact with memantine include procainamide, quinine, anticholinergics, L-dopa and dopaminergic agonists (drugs such as bromocriptine, ropinirole, pramipexole), ketamine, dextromethorphan (DM), and anti-coagulant blood thinner medications taken by mouth.

Anticoagulants:
Memantine may interact with anticoagulants. Prothrombin time and/or INR should be monitored closely in patients taking anticoagulant medication

If any of the medications above must be used, patients should be monitored for signs of memantine toxicity including lethargy, hallucinations, tremor, agitation and insomnia.

7.6.2 Not Permitted

Cytotoxic chemotherapy will be ceased at least 48 hours before radiation treatment and will be re-started at least 48 hours after radiation treatment for both arms. Investigators should use best judgment and available data to determine the most appropriate interval between radiation treatment and specific anti-cancer therapies. At the investigators discretion, non-cytotoxic anti-cancer drugs, including immunotherapy agents, may be delivered concurrently with SRS and WBRT.

BRAF inhibitors used during HA-WBRT are permitted at the investigators’ discretion, but interruption of the BRAF inhibitor during HA-WBRT should be considered.

Current use of NMDA antagonists, such as amantadine, ketamine, or dextromethorphan, is not permitted while receiving protocol therapy.
8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Evaluable for Adverse Events.* All patients will be evaluable for adverse event evaluation from the time of their first treatment.

8.1.2 *Evaluable for Overall Survival.* All patients will be evaluable for overall survival from the time of randomization.

8.1.3 *Evaluable for Progression Free Survival by Neurocognitive Assessment.* All patients who have completed the neurocognitive assessment are evaluable for cognitive deterioration free survival.

8.1.4 *Evaluable for Disease Control/CNS Failure.* All patients who have received any part of the protocol radiation/radiosurgery, and have their disease re-evaluated, will be considered evaluable for response.

8.1.5 *Evaluable for Quality of Life.* All patients who have completed the quality of life questionnaire are evaluable for quality of life.

8.2 Response and Evaluation Endpoints

The MRI at each evaluation will be scored according to the RANO-BM criteria [Lin 2015]:

Complete response: Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.

Partial response: At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.

Stable disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.

Disease progression: At least a 20% increase in the sum longest diameter of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
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CCTG TRIAL: CE.7

<table>
<thead>
<tr>
<th></th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target lesions</strong></td>
<td>None</td>
<td>≥ 30% decrease in sum longest distance relative to baseline</td>
<td>&lt; 30% decrease relative to baseline but &lt; 20% increase in sum longest distance relative to nadir</td>
<td>≥ 20% increase in sum longest distance relative to nadir*</td>
</tr>
<tr>
<td><strong>Non-target lesions</strong></td>
<td>None</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Unequivocal progressive disease*</td>
</tr>
<tr>
<td>New lesion(s)**</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present*</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>None</td>
<td>Stable or decreased</td>
<td>Stable or decreased</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Clinical Status</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Stable or improved</td>
<td>Worse*</td>
</tr>
<tr>
<td>Requirement for response</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>Any***</td>
</tr>
</tbody>
</table>

* Progression occurs when this criterion is met.
** A new lesion is one that was not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow up assessment will determine if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of initial scan showing the new lesion.
*** Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

8.3 **Response Duration**

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

8.4 **Stable Disease Duration**

Stable disease duration will be measured from the time of randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

8.5 **Overall Survival**

All randomized patients will be included in the analysis of overall survival, which is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive.

8.6 **Time to CNS Failure**

Time to CNS failure will be measured from the date the patient is randomized on this study to the date of diagnosis of disease progression.
9.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix IV). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site:

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all “reportable” serious adverse events are subject to expedited reporting using the CTEP-AERs reporting system (which may be accessed via the EDC system). See Section 9.1 for details.

9.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 9.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the investigator brochure.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

9.2 Expedited Adverse Event Reporting Instructions

This study requires that expedited adverse events be reported to CCTG using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP’s guidelines for CTEP-AERS can be found at http://ctep.cancer.gov

CTEP-AERS Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP website (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the “NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs” which can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 10.3.4).
In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Please also contact the CCTG Study Coordinator by telephone at 613-533-6430. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

9.3 Routine Adverse Event Reporting

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

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. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

9.4 Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting

9.4.1 Pregnancy Prevention

Women of Childbearing Potential (WOCBP) and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criteria. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

9.4.2.1 Pregnancy Reporting for Canadian sites

The investigator is required to report to CCTG and CTEP any pregnancy occurring in participants and pregnancy in partners of participants. Pregnancies occurring up to 90 days after the completion of study treatment must also be reported.

The investigator should report the pregnancy within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage, under the “Toolbox” link. The pregnancy must also be reported within 24 hours of learning of the pregnancy via CTEP-AERS. In addition to the submission of a CTEP-AERS report, the investigator is also required to complete the Pregnancy Information Form and fax to CTEP at 301-230-0159 and CCTG at 613-533-2812 or by Email at safety-desk@ctg.queensu.ca.

The pregnancy reporting forms should be updated to provide the outcome of the pregnancy. All follow-up reports must be submitted to CCTG and CTEP in a timely manner.

Information from the trial participant’s pregnant partner can only be collected following informed consent. A copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG. Centres that require additional informed consent for the pregnancy notification and/or outcome from a pregnant trial participant or about the pregnant partner must submit a copy of the signed signature page of the Pregnancy Follow-up consent to CCTG.

Additional information regarding the CTEP requirements (including guidance on grades, Standard of Care (SOC), the Pregnancy Information Form and other reporting instructions) can be found in the “NCI Guidelines for Investigators: Adverse event reporting requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs” document.

9.4.2.2 **Pregnancy Reporting for United States (US) sites**

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

9.4.3 **Exposure Reporting (Non-study Participants) for Canadian Sites**

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non-study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure, ideally within 24 hours of learning of the exposure using the CCTG Exposure Reporting Form available from the trial webpage under the “Toolbox” link.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual from the time of exposure until 30 days after exposure. All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the exposure results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

9.5 **CCTG Responsibility for Reporting Serious Adverse Events to Health Canada**

The CCTG will provide expedited reports of SAEs to Health Canada for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected (as determined by reference to the Product Monograph), AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

9.6 **Reporting Safety Reports to Investigators**

CCTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the CCTG trial CE.7 web-based safety monitoring utility.
Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial CE.7 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of these events to your ethics board should be done as soon as possible we suggest within 30 days. REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.
10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 7.0.
- Request by the patient.
- Completion of therapy as outlined in Section 7.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Therapy After Protocol Treatment is Stopped

After protocol treatment is stopped, therapy is at the discretion of the investigator.

10.3 Follow-up Off Protocol Treatment

Refer to Section 5 for details of follow up and required investigations after protocol therapy has been stopped. Patients who have progressed will continue with evaluations detailed in Section 5, and a Progression report should also be completed.

Annual minimal follow up using the Short Follow-up Report is required for patients who have not received any protocol therapy. Ineligible patients who have received at least one dose of protocol therapy should be followed as per protocol guidelines outlined in Section 5.
11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Data Review

CCTG receives core support from the Canadian Cancer Society. To ensure efficient use of limited funding, the CCTG has, over the past 40 years, optimized their risk based trial oversight and monitoring program. A critical component is central data review of submitted deidentified source documents, allowing source data verification and confirmation of key aspects including eligibility, endpoints and safety outcomes. Depending on the trial’s design, these source documents may include such source documents as surgical and histopathology reports to confirm disease stage and type, imaging reports to confirm extent of disease and assess efficacy, or include submission of tumour samples (to confirm diagnosis and eligibility or DICOM images (to verify response or radiation therapy planning). These source documents are reviewed by experienced data managers and physicians and are critical to ensuring the accuracy of the data and consistency of conclusions drawn.

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients’ charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP). This application is available on the CTSU members’ website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with the CRA or Investigator roles in Rave can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU members’ website under Auditing & Monitoring > Source Document Portal in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

See Appendix III (Documentation for Study) for details of supporting document requirements for this trial and for requirements for the redaction of personal identifiers. Although it remains the centres responsibility to ensure adequate redaction of any information provided to CCTG, submitted source documents are reviewed prior to acceptance at CCTG; in the case of incomplete redaction, documents are removed and the site assigned a violation and required to resubmit.

All patients will provide written informed consent for submission of source documents, and the rationale and documents to be collected will be detailed in the informed consent document.

11.2 Central Radiology Review

All images will be submitted for detailed imaging analysis to be reviewed centrally.
**MRI Data Archiving, Storage, and Submission**

The complete MR imaging data sets must be submitted/uploaded to the American College of Radiology (ACR) Transmission of Imaging and Data (TRIAD) system in DICOM format, within no more than 5 business days post MR image acquisition or when trial patient pre-registration is completed. BMP files, JPEG files, or hard copies (films) are not acceptable. The MRI Submission Form (from EDC) and Tumour Measurement Worksheet summarizing the disease information must be submitted together with the entire MRI DICOM data set.

De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the patient ID number and protocol number. The de-identified digital images may then be submitted/uploaded in the system for further electronic data transfer purposes.

This central image review will not be done in real-time. The image analysis will include evaluation of any discrepancy between the imaging protocol used and the recommended imaging protocol (provided in the accompanied imaging pamphlet). Additional imaging parameters that will be documented include the spatial resolution, magnet strength (1.5 T vs. 3 T), and gadolinium contrast dose and relaxivity. Sites will be asked to report whether a dedicated neuroradiologist was involved in interpretation of the treatment planning MRI. All these parameters will be evaluated for their impact on local and distant brain control.

On conventional MRI, changes in the following measures will be calculated: (i) magnitude and rate of change in the volume of T2 hyperintensity (ii) baseline and changes in volume of the brain and subvolumes (e.g. Hippocampus, frontal lobe). The association between cognitive function and these volumes at baseline and changes in these volumes will be evaluated.

11.3 **Central Pathology Review**

There will be no central pathology review for this study.

11.4 **Central Radiotherapy Review**

Please refer to Section 7.0.
12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual will be provided on the CE.7 trial specific website, which will include details regarding sample preparation, handling and shipping.

Specimens collected may be used by researchers now or in the future to better understand the nature of cancer, and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial the surgical/histology number and/or patient initials. Material issued to researchers will be anonymized and only identified by a coded number.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

12.1 Protocol-Mandated Correlative Studies

Blood, Serum, Plasma and Urine Collection

The submission of whole blood, serum, plasma and urine is mandatory for participation in this trial. Failure to submit these samples as directed in Section 5 of the protocol, and as per the laboratory manual, will result in the patient being considered ineligible. Please consult the lab manual for details of specimen collection, processing and shipment for this purpose.

The primary goal is to evaluate whether molecular/genomic biomarkers (i.e., somatic mutations) in liquid biopsy can enhance prediction of the overall survival and development of new brain metastases in patients with five or more brain metastases who receive SRS compared to patients who receive WBRT. The secondary goal is to evaluate differences of molecular genomics (i.e., somatic mutations) of liquid biopsy samples at baseline and changes by primary tumour sites. The tertiary goal is to investigate molecular/genomic mechanisms (e.g. CRP and BDNF) of neurocognitive decline and radiographic changes.

Whole blood will be collected in Streck tubes and processed for the purpose of cell free DNA analysis. This, as well as additional whole blood, plasma, serum, and urine samples, will be collected prior to the start of protocol therapy, immediately after RT, and then at 8 weeks, 4 months, 6 months, and 12 months post treatment.

Submission of additional whole blood, plasma, serum and urine for the purposes of banking/future research is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. These samples will be collected at the same time as the cell free DNA samples, processed at the sites and will be carefully banked as part of the CCTG tissue/tumour bank at Queen’s University in Kingston, Ontario.

At the specified times, participants will provide the following blood specimens: STRECK tubes (whole blood in EDTA for cell free DNA extraction), lavender topped tubes (whole blood in EDTA), light green topped tubes (containing lithium heparin - for plasma), and red topped tubes (for serum).

Specimens will be processed and stored at participating centers immediately after collection and then shipped to a central laboratory, frozen on dry ice, in batches of 10 sets or more (1 set = entire blood collection at one patient visit), for subsequent storage and future analysis. Please consult the lab manual for specimen collection and shipping details.
CIRCULATING TUMOUR DNA (ctDNA):
We will use QIAamp Circulating Nucleic Acid Kit to isolate cell free DNA from plasma. With anticipated limited amount of DNA can be obtained from ctDNA, we will apply a focused next-generation sequencing approach using the Qiagen Human Comprehensive Cancer GeneRead DNAseq Targeted Panel V2 (Qiagen) with 10 ng DNA input. This panel targets the enrichment of the coding (exonic) regions of 160 cancer-related genes that are most commonly mutated in cancers with a recognizable oncogenic consequence. This panel covers 20 genes commonly mutated in lung cancer and 44 genes most commonly mutated in breast cancer. More importantly, this panel covers mutations of 24 clinically-relevant genes, including AKT1, ALK, AR, BRAF, CTNNB1, DDR2, EGFR, ERBB2, FGFR3, GNA11, GNAQ, IDH1, IDH2, KIT, KRAS, MAP2K1, MET, NRAS, PDGFRA, PIK3CA, PTEN, RET, STK11, and TP53. Next generation sequencing (NGS) will be carried out using an Illumina MiSeq desktop sequencer. Qiagen Cloud-Based DNAseq Sequence Variant Analysis software will be used to analyze the GeneRead NGS data according to the manufacturer’s instructions. Final somatic mutation data will be merged with clinical data for subsequent statistical analysis. To have rapid clinical application, we plan to obtain funding to perform Guardant360 cell-free DNA (cfDNA) assay for somatic mutations detection with digital sequencing methodology.

SERUM CRP AND BDNF:
We will use the High-Sensitivity CRP ELISA Kit (CR120C; Calbiotech, Spring Valley, CA) to measure CRP levels and Human BDNF ELISA Kit (ab99978; Abcam, Cambridge, MA) to measure BDNF levels at different time points. Final biomarker data will be merged with clinical data for subsequent statistical analysis.

12.2 Optional Banking of Samples

Banking of Blood, Serum and Plasma
Mandatory submission of whole blood, serum, and plasma (and urine) has been described above. The subsequent banking of collected samples is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Samples will be carefully banked as part of the CCTG tissue/tumour bank at Queen’s University in Kingston, Ontario.

Urine samples will be stored and used for studies of radiotherapy-related changes of metabolomics and oxidative DNA damage, such as 8-hydroxydeoxyguanosine (8-OHdG).
Proposals to use the banked specimens for the purposes of assessing markers involved in predicting treatment response and outcomes may be submitted to the bank. A scientific review process of any proposals to use the banked samples will take place and any proposals approved will have undergone ethics approval.
13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

This is a prospective, randomized, multi-center study in patients with five or more brain metastases. The primary objectives are to compare the effect between the treatments of SRS versus HA-WBRT plus memantine on the neurocognitive progression-free survival (NPFS) and overall survival (OS) in the study population. Patients will be randomized at a 1:1 ratio to two study treatment arms, stratified by DS-GPA predicted median overall survival (< 6 months vs. ≥ 6 months), use of targeted or immunotherapy within 4 weeks of original diagnosis of brain metastases/planned for within 4 weeks of radiation therapy (yes or no), Histology (radio-resistant vs. other), and Metastasis within 5 mm of hippocampus (Yes vs. No).

Secondary objectives include to compare time to CNS failure; validate the performance of a CNS failure nomogram; to evaluate if there is any difference in CNS failure patterns (local, distant, or leptomeningeal) in patients who receive SRS compared to patients who receive HA-WBRT plus memantine; to evaluate number of salvage procedures following SRS in comparison to HA-WBRT plus memantine; to evaluate the individual cognitive test results following SRS in comparison to HA-WBRT plus memantine; To tabulate and descriptively compare the post-treatment adverse events associated with the interventions; to evaluate the time delay to re-initiation of systemic therapy in patients receiving SRS in comparison to HA-WBRT plus memantine; to evaluate the toxicity and safety of the study treatments, to compare the quality of life (QoL), health economics between treatment arms; and to evaluate the prognostic and predictive translational biomarkers and Imaging/dosimetric endpoints.

13.2 Primary Endpoints and Analysis

A co-primary endpoint is neurocognitive progression-free survival, which will be measured from the date the patient is randomized to the date at which there is a drop of at least 1.5 standard deviations from baseline in at least two of the core six neurocognitive test scores (all tests are standardized based on published norms), or the date of death for patients who died without documented neurocognitive progression. For patients with inadequate/incomplete baseline neurocognitive assessment or for whom no neurocognitive re-evaluation was performed after baseline / randomization, will be censored at the date of randomization. For patients with adequate baseline neurocognitive assessment and at least one post-baseline neurocognitive assessment, but where one or more planned subsequent neurocognitive re-evaluations were missed, will be treated as having neurocognitive progression at the time of the first missed assessment for which no subsequent assessment exists before the declared date of analysis showing absence of neurocognitive progression. All other patients alive at the declared date of analysis who have completed planned neurocognitive assessments and have not demonstrated neurocognitive progression will be censored at the date of last neurocognitive evaluation.

It is strongly encouraged to have the in-person evaluation of the neurocognitive test scores. However, in case that the extreme conditions make the in-patient evaluation not possible, the Oral TMT is acceptable. It should be pointed out that the in-person evaluation TMT scores and oral TMT scores will be standardized separately, evaluating the change in the TMT score accordingly.
The other co-primary endpoint is overall survival. Survival time will be measured from the date of randomization to the date of death, due to any cause. Death will be scored either as due to neurological cause (any CNS event such as an intracranial mass, hemorrhage, or hydrocephalus) or non-neurological cause but all causes of death will be considered in the primary endpoint.

Efficacy analysis will be based on the intention-to-treat principle with all randomized patients belonging to the treatment arm to which they were randomized unless pre-specified otherwise. The distribution of neurocognitive progression free survival for both treatment arms will be estimated using the Kaplan-Meier method, and their difference will be tested using the log-rank test stratified by patient cohorts accrued pre/post hippocampal sparing to where it applies and selected stratification factors of DS-GPA predicted median overall survival (< 6 months vs. ≥ 6 months); Use of targeted or immunotherapy within 4 weeks of original diagnosis of brain metastases, or planned for within 4 weeks of radiation therapy (yes or no) at randomization. Cox proportional hazards model adjusted for all stratification factors will be used to estimate the hazard ratios along with its 95% confidence intervals. Median of NPFS and its 95% C.I. will be estimated using the method of Brookmeyer and Crowley.

Overall survival will be analysed similarly to the NPFS with the estimated corresponding 95% upper confidence bound of the estimated HR.

The co-primary endpoints will be considered jointly in making the conclusion for this study:

1. If the Null Hypothesis I is rejected indicating superiority of SRS in neurocognitive progression-free survival and/or the Null Hypothesis II is rejected indicating SRS is superior in overall survival, this study would establish SRS as the standard of care for patients with 5 or more metastases.

2. If the Null Hypothesis I is rejected indicating superiority of SRS in neurocognitive progression-free survival while the Null Hypothesis II is not rejected indicating SRS is equivalent or inferior in overall survival, then SRS may still have clinical use due to its advantage in neurocognitive progression-free survival. In conjunction with economic data, this study will provide level I evidence to assist in making therapeutic decisions.

3. If neither Null Hypotheses are rejected indicating that SRS is not superior in either neurocognitive progression-free survival or overall survival, then HA-WBRT plus memantine would be clarified as the standard of care for patients with more than 4 metastases.

Secondary endpoints to be examined include survival free of WBRT, time to CNS failure, performance of a CNS failure nomogram. For all the time to events endpoints, they will be analyzed similarly to the primary endpoints of NPFS. Cumulative incidence of clinically significant local events (grade 2 or higher clinical severity on the CTCAE scale for either symptomatic local recurrence or radionecrosis).

Safety Analysis

Safety Analysis will be performed based on as-treated population. All patients who have received at least one dose/fraction of study treatment will be included in the safety analysis. The incidence of adverse events will be summarized by type of adverse event and severity using the current NCI Common Terminology Criteria for Adverse Events. A Fisher’s exact test will be used to compare adverse events between the study new treatment and the standard control arms if required.
13.3 Sample Size and Duration of Study

The Null Hypothesis I in this study is: SRS is equivalent or inferior to HA-WBRT plus memantine in terms of neurocognitive progression free survival post-radiation versus the alternative that SRS is superior to HA-WBRT plus memantine.

We assume that the proportion of patients with neurocognitive progression at the 6 month post-registration evaluation is 70% for patients undergoing HA-WBRT plus memantine. In order to detect a 40% risk reduction in the risk of the neurocognitive progression (reduce the 6-month event rate of 70% to around 51.4%), using a 5% significance level 2-sided test with 90% power, we need to randomize 196 patients with a 1:1 ratio to either treatment arm in 4 years, and the required number of events for the final analysis (163) will be observed with another 6 months follow up. The 10 patients accrued before hippocampal-avoidant is included as standard care will be excluded from the primary analysis of NPFS, which makes the total sample size of 206.

As a sensitivity analysis, we will perform a cause-specific analysis of neurocognitive progression with death without neurocognitive progression as a competing risk. Gray’s test will be used to test the difference in the cumulative probability of neurocognitive failure [Gray 1988]. The cause-specific Cox proportional hazards regression model will be used to evaluate the treatment effect. Based on outcome of NRG CC001, it was estimate that approximately 30% of events are anticipated to be death without neurocognitive progression, we can detect a cause-specific HR of 0.59 with 80% power in this sensitivity analysis.

The Null Hypothesis II in this study is: SRS is inferior to HA-WBRT plus memantine (HR = 1.25) in terms of overall survival versus the alternative hypothesis that SRS is marginally superior to HA-WBRT plus memantine. The estimated median OS in patients with adjuvant HA-WBRT plus memantine is 7.5 months and the median OS for patients with SRS is approximately 8.8 months. Thus, we assume that SRS would result in a marginal improvement in OS, with approximately a 15% reduction in hazard of death over HA-WBRT plus memantine. Using the design proposed by Freidlin et al [Freidlin 2007] for the calculations, the sample size of 206 patients will give us an 80% chance to rule out the upper 95% confidence bound of hazard ratio of the risk of death of SRS versus HA-WBRT plus memantine is greater than 1.25. In other words, the trial will have 80% power with 0.95 probability of ruling out that the hazard ratio of SRS versus HA-WBRT plus memantine with respect to OS is 1.25 or higher (in favour of HA-WBRT) if the true hazard ratio is 0.85 (in favour of SRS). The total expected events of deaths are 167.

13.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators’ meetings.

13.5 Interim Analysis

Futility analyses for hypothesis I and hypothesis II will be performed at the time of 140 patients have accrued to the study — approximately 2 years after the study starts to accrue (at a time when 40% of the total information has been accumulated). For the neurocognitive progression free survival and overall survival analysis, if we observed a hazard ratio (HR) of no less than 1 in comparison of SRS to HA-WBRT plus memantine in neurocognitive progression free survival, or observed a HR of no less than 1.25 in comparison of SRS to HA-WBRT plus memantine in overall survival, we would stop the trial as the SRS is unlikely to have potential target effect that the trial was designed to detect. Otherwise, continue the trial for final analysis.
13.6 **Quality of Life Analysis**

The quality of life (QoL) of patients will be assessed using the EORTC QLQ-C30 in conjunction with the brain module QLQ-BN20. These are validated QOL instruments. ECOG performance status, and EQ-5D-5L will also be considered as part of QoL analysis.

The QOL data will be analyzed to look for statistically and clinically significant differences between the study treatments versus the standard treatment groups.

The Null Hypothesis in this study will be: SRS is equivalent or inferior to HA-WBRT plus memantine in terms of Quality of Life post-treatment versus the alternative that SRS is superior to HA-WBRT plus memantine post-treatment.

The primary time points of interest will be at 2, 4 and 6 months post treatment as these are the most likely times where differences may be observed between the 2 arms. The minimal important difference will be set at 10 points and distribution-based minimal clinically important differences estimates at 0.5 SD [Wong, 2015].

QOL measurements will also be compared at each time point across both arms. In addition, changes from baseline and each follow-up endpoint will be compared across the arms. The standard CCTG QoL Response Analysis categorizing patients as either having improved, stable, or worsened QoL will be used. A change score of 10 points from baseline is defined a priori as clinically relevant. For functional scales and global health status, patients will be considered to have QoL improvement if reporting a score of 10-points or better than baseline at any time of QoL assessment. Conversely, patients will be considered worsened if reporting a decrease in score of 10-points or worse than baseline at any time of QoL assessment without above defined improvement. Patients whose scores fall between 10-point changes from baseline at every QoL assessment will be considered as stable. In contrast to functional scales, for the determination of patient’s QoL response, classification of patients into improved and worsened categories will be reversed for symptom scales.

Missing data will be handled in a number of ways. First, all analyses will be run using only the data available. Second, imputation will be carried out by use of last-value-carried forward (LVCF), average-value-carried forward (AVCF) and nearest neighbor. Collectively, these four approaches have been demonstrated to be useful for identifying the impact of missing data on results as long as the amount of missing data is no more than 20%.

13.7 **Economic Analyses**

The purpose of the CCTG economic evaluation is to compare the estimated cost of brain-related therapies in patients who receive SRS compared to patients who receive HA-WBRT plus memantine from a payer perspective (Medicare for US / provincial heath authorities in Canadian jurisdictions with activity-based funding), over a lifetime time horizon by prospectively collecting economic and resource utilization information as well as health utilities during the trial.

The robustness of the model results will be assessed using one-way and multi-way sensitivity analyses. Major drivers of medical care costs, such as surgery, hospitalization, radiotherapy and survival, will be varied ± 20%, to examine the impact on the estimated costs. Bootstrapping method will be used for estimate of C.I.
Radiotherapy Quality Assurance Analyses

The purpose of the CCTG radiotherapy quality assurance evaluation is to ensure that the treatment can be delivered safely for this group of patients who have historically not commonly received SRS or HA-WBRT. Radiotherapy quality assurance endpoints will include 1) measuring the frequency with which lesions that were overlooked on the treatment planning imaging become apparent in follow-up and require additional treatment. 2) calculating the risk of radionecrosis as a function of the number of lesions treated, the location of the treated lesions, the total volume of lesions treated and the normal brain/brain V12. 3) assessing the frequency of deviations in contouring and IMRT planning for HA-WBRT during credentialing and pre-/post-treatment case reviews.

Image Analysis

Exploratory analyses on the Impact of the Quality of Image Acquisition and Utilization on Outcomes will be performed based on all patients evaluable for the imaging sub-study.

The purpose of the image analyses is to evaluate impact of the quality of image acquisition based on conformity with the recommended imaging protocol and quality of image utilization (i.e. dedicated neuroradiology review of the treatment planning images) on clinical outcomes including intracranial and local control following radiosurgery treatment.

Image acquisition conformity will be evaluated as follows:
1. Image acquisition parameters (DICOM headers) are within the recommended acquisition protocol.
2. Image distortion evaluation of the treatment planning MR.

Cox regression model will be used to explore the correlation of image acquisition conformity with time to CNS progression in patients treated with SRS or HA-WBRT.

The second major goal of the image analyses is to evaluate whether baseline or change in volume of white matter hyperintensity or brain substructures are associated with neurocognitive decline following SRS or HA-WBRT.

The volumes of the following regions of interest and structures will be measured at each time point longitudinally:
1. T2-hyperintense areas in the brain as a sum volume.
2. Right and left hippocampi.
3. Whole brain volume.

The relationship between the baseline volumes of these structures and baseline cognitive scores and the relationship between changes in volumes of these structures and longitudinal changes in cognitive scores will be evaluated using linear mixed effects models.
14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc.

14.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group and Alliance and NRG Oncology may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.
- In the event of a separate paper dealing with economic analysis outcomes, the first author will generally be the Economic Analysis Coordinator on the trial committee.
- In the event of a separate paper dealing with radiotherapy quality assurance outcomes, the first author will generally be the Radiation Therapy Quality Assurance Coordinators on the trial committee.

14.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

"A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

14.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

14.3 Submission of Material for Presentation or Publication

Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator’s confidential and proprietary data, in addition to Collaborator(s)’s intellectual property rights, are protected. Copies of abstracts should be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release.
15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

15.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

This study is affiliated with the US National Cancer Institute (NCI US). Therefore, the conduct of this study must comply with the US regulations regarding the Protection of Human Subjects (Title 45, Part 46, US Code of Federal Regulations).

15.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre’s responsibility to ensure compliance with all local SOPs.

It is CCTG’s policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject’s competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).
Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

15.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant’s/potential participant’s willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

15.3.1 Obtaining Consent for Pregnancy Reporting

Information from the subject (i.e. the pregnant female) should not be collected from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the main consent form adequately addresses the pregnancy notification and collection of information regarding the outcome of a pregnancy of a trial participant, a “Pregnancy Follow-up” consent form will not be required by CCTG. CCTG also considers the main consent form signed by the trial participant adequate consent for notification and collection of the outcome of a pregnancy of a trial participant’s pregnant partner. Any information collected from the trial participant’s pregnant partner can only be collected following their informed consent.

A trial-specific consent form for “Pregnancy Follow-up” can be found on the trial webpage. The consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner).
Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

15.3.2 **Obtaining Consent for Exposure Reporting - Canadian Sites Only**

Information from and/or about the subject (i.e. the exposed individual) should not be collected from and/or about them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about and/or from them.

A trial-specific consent form for “Exposure Follow-up” can be found on the trial webpage. The consent form must be used to obtain consent from any non-trial participant (such as the exposed individual).

Participants will not be withdrawn from the main trial as a result of a refusal or withdrawal of permission to provide information related to the exposure.

15.3.3 **Obtaining Consent for Research on Children – Canadian Sites Only**

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/guardian.

For reporting an exposure, the parent/guardian is required to sign an “Exposure Follow-up” consent form (even if they are a participant in the main study) prior to collecting information about the child.

15.4 **Discontinuation of the Trial**

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

15.5 **Retention of Patient Records and Study Files**

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by CCTG that documents no longer need to be retained.
In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

For international participating regions, local regulatory guidance should be followed with respect to duration of records retention, unless otherwise contractually dictated.

15.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

15.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

The above mentioned documentation, in addition to any submitted source documents, may be accessed remotely in the event of a public health emergency either through remote access to Electronic Medical Records or through a secure file sharing portal.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

As the trial is NCI US affiliated, the findings will be reported to the NCI US Clinical Trials Monitoring Branch as required.

15.8 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s).

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution’s data safety monitoring plan.
15.8.1 \textit{Method}

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

\textbf{Note:} Serious adverse events must be submitted via CTEP-AERS per protocol guidelines.
16.0 REFERENCES


APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

*Karnofsky and Lansky performance scores are intended to be multiples of 10.*

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Score</th>
<th>Description</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
<td>100</td>
<td>Normal, no complaints, no evidence of disease.</td>
<td>100</td>
<td>Fully active, normal.</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease.</td>
<td>90</td>
<td>Minor restrictions in physically strenuous activity.</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.</td>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease.</td>
<td>80</td>
<td>Active, but tires more quickly.</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>Cares for self, unable to carry on normal activity or do active work.</td>
<td>70</td>
<td>Both greater restriction of and less time spent in play activity.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
<td>60</td>
<td>Requires occasional assistance, but is able to care for most of his/her needs.</td>
<td>60</td>
<td>Up and around, but minimal active play; keeps busy with quieter activities.</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Requires considerable assistance and frequent medical care.</td>
<td>50</td>
<td>Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.</td>
<td>40</td>
<td>Disabled, requires special care and assistance.</td>
<td>40</td>
<td>Mostly in bed; participates in quiet activities.</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Severely disabled, hospitalization indicated. Death not imminent.</td>
<td>30</td>
<td>In bed; needs assistance even for quiet play.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
<td>20</td>
<td>Very sick, hospitalization indicated. Death not imminent.</td>
<td>20</td>
<td>Often sleeping; play entirely limited to very passive activities.</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Moribund, fatal processes progressing rapidly.</td>
<td>10</td>
<td>No play; does not get out of bed.</td>
<td></td>
</tr>
</tbody>
</table>

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.*
APPENDIX II - DRUG DISTRIBUTION, SUPPLY AND CONTROL

General
Memantine is not being supplied for this study. Canadian and US sites will use their own commercially available marketed supply.
APPENDIX III - DOCUMENTATION FOR STUDY

Data Submission/Data Reporting:

Follow-up is required for patients from the time of randomization.

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

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

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

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members’ website under Data Management > Rave Home and click to accept the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the centre of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will replace the eLearning link under the study name.

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

Digital RT Data Submission Using TRIAD:

Refer to Section 7.5 for instructions on how to submit documents to TRIAD.
The ELECTRONIC CRFs to be used in this trial, through the EDC system, are as follows:

<table>
<thead>
<tr>
<th>Electronic Folder</th>
<th>Required at</th>
<th>To be completed electronically</th>
<th>Supporting Documentation Required*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Checklist</td>
<td>Required within 2 weeks of randomization</td>
<td></td>
<td>Consent form**</td>
</tr>
<tr>
<td>Baseline Report</td>
<td>Required within 2 weeks of randomization</td>
<td></td>
<td>Diagnostic pathology &amp;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>protocol-mandated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>baseline radiology reports,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tumour measurement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>worksheets (TMS)</td>
</tr>
<tr>
<td>Correlative Studies Report</td>
<td>Required within 2 weeks of visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Tumour and Blood)</td>
<td>See Section 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment Report</td>
<td>Required within 2 weeks of end of cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of Treatment Report</td>
<td>Required within 2 weeks of end of treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 Week Follow-up Report</td>
<td>Required within 2 weeks of the visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up Report</td>
<td>Required within 4 weeks of the visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse/Progression Report</td>
<td>Required within 4 weeks of progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Follow-up Report</td>
<td>See Section 5</td>
<td>Required within 4 weeks of the visit</td>
<td>Autopsy report, if performed</td>
</tr>
<tr>
<td>Death Report</td>
<td>When patient passes away</td>
<td>Required within 4 weeks of the patients death</td>
<td></td>
</tr>
<tr>
<td>SAE Report***</td>
<td>At time of event</td>
<td>Required within 1 working day</td>
<td>Additional clinical, laboratory</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>or imaging reports that</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>may inform evaluation of safety</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>including, admission and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>discharge summaries/notes</td>
</tr>
</tbody>
</table>

* Scan and upload using the Source Document Portal (SDP) on the CTSU website. Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Supporting documents should be uploaded immediately after the report they refer to has been submitted electronically. EDC forms submitted without supporting documentation are not considered submitted and will be reflected in the Centre Performance Index (CPI) as not submitted. All patient identifiers, other than the CCTG patient ID assigned at enrollment, and any other prohibited personal information must be fully and completely redacted (blacked-out) on all source documentation, per national and local privacy protection regulations and requirements. Acceptable methods include:
  - **fully opaque** sticker/tab placed over the identifiers prior to scanning
  - **fully opaque** black marker; prior to upload please ensure that the information is no longer visible on the scanned document
  - electronic black box placed over identifiers in PDF document that is subsequently printed and then scanned. (*NOTE: do not send the unprotected PDF file with black boxes included as those can be moved/removed easily after opening*)
  - electronic stripping of identifiers prior to upload (typically only possible for DICOM images)

Note that supporting documents must include the participant’s trial code, CCTG patient serial number, and participant initials (or a two/three masking letter code assigned by your centre).

** Required for Canadian centres, it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated. Centres are expected to redact the participant’s name and signature on the submitted copy, leaving only a portion visible (e.g. initials or loops) to confirm that a person has signed but that cannot identify that individual.

*** See Section 9.0 Serious Adverse Event Reporting for details.

Note that MRI image documents and treatment planning and delivery information must be uploaded using TRIAD, as well as documents for the purpose of RTQA approval. Please consult the RTQA Manual for required documents for RTQA approval and treatment reviews.
Documents to be uploaded into TRIAD include:

- Anatomic MR images at pre-registration (i.e. diagnostic MRI obtained within 30 days prior to randomization)
- Image for the planning MRI (or CT, or both) acquired within 14 days prior to the start of treatment.
- Anatomic MR images obtained at 8 weeks, 4 months, 6 months, 9 months, 12 months, 16 months and 24 months, and then annually after protocol therapy.
- Pre-Treatment Local Review of SRS and HA-WBRT delivery

For each anatomic MRI image document submission, please be sure to include the complete MR image data sets, including the MRI Submission Form (from EDC), the MRI report, and the Tumour Measurement Worksheet summarizing the disease information.

Please note that BMP files, JPEG files, or hard copies (films) are not acceptable.

The collection of the following information will involve the combination of paper and electronic forms, as follows:

<table>
<thead>
<tr>
<th>Data</th>
<th>Required at</th>
<th>Collection/Submission</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life Questionnaire (QLQ-C30 + BN20)</td>
<td>Randomization: within 14 days prior to randomization*</td>
<td>Patient to complete on paper; site to enter relevant data (as required) in the EDC system within corresponding folders</td>
<td>Retain questionnaires at the site.</td>
</tr>
<tr>
<td>EQ-5D-5L Questionnaire</td>
<td>After protocol treatment, as follows:</td>
<td>See Appendix VII for submission instructions of completed neurocognitive booklets.</td>
<td></td>
</tr>
</tbody>
</table>
| Neurocognitive Assessments    | • Week 8, 4 months, 6 months, 9 months, 12 months, 16 months, 24 months, then every 12 months  
  • At the time of disease progression |                                                                             |                                   |
|                               | * The EORTC QLQ-C30+BN20, and EQ-5D-5L questionnaires, as well as the neurocognitive assessments, should only be administered to patients who have provided consent. These should be completed/administered after registration and prior to the start of protocol therapy (i.e. within 14 days prior to randomization). |

Data Quality Portal:

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

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

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.
To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status and DQP Reports modules.

This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display N/A for the Total Delinquencies summary count.
APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website:
APPENDIX V - QUALITY OF LIFE ASSESSMENT

The Quality of Life Assessment documents, including the QLQ-C30 + BN20 and the Health Utilities Index (EQ-5D), will be made available on the trial website. Questionnaire booklets are to be completed during the scheduled clinic visits and returned to study staff.

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

• additional and useful information may be obtained from quality of life measurements
• a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

• to try to achieve the best possible outcome for patients
• to evaluate the extent of change in the quality of life of an individual or group across time
• to evaluate new treatments and technologies
• to support approval of new drug applications
• to try to provide the best value for health care dollars
• to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

Quality of life data are collected for research purposes, and will usually not be used for the patient’s individual medical care. The assessment is in the form of a self-report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the “correct” answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

• pre-randomization or pre-registration (baseline)
• during treatment
• during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.
If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient’s life, e.g.: psychological distress, social disruption, side-effects, et cetera.

The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life questionnaire should be given to the patient before being seen by the doctor, as required by the schedule in the protocol (not required during treatment for this trial).

4. Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

*It defeats the whole purpose of the assessment if it is delayed until the patient feels better!*

5. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.
Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if s/he cannot comprehend either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.
8. **Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)**

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.
Quality of Life Questionnaire – ENGLISH

CCTG Trial: CE.7

This page to be completed by the Clinical Research Associate

### Patient Information

<table>
<thead>
<tr>
<th>CCTG Patient Serial No: __________</th>
<th>Patient Initials: _____ _____ _____ (first-middle-last)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution: ____________________</td>
<td>Investigator: __________________________________________</td>
</tr>
</tbody>
</table>

Scheduled time to obtain quality of life assessment: please check (√)

- [ ] Prior to randomization
- [ ] Off Treatment - prior to, or within 2 weeks of progression only:
  - [ ] week 8
  - [ ] month 4
  - [ ] month 6
  - [ ] month 9
  - [ ] month 12
  - [ ] month 16
  - [ ] month 24
  - [ ] month 36
  - [ ] month 48
  - [ ] month 60
  - [ ] month ___

Were ALL questions answered?  ____ Yes  ____ No  If no, reason: ____________________________________________

Was assistance required?  ____ Yes  ____ No  If yes, reason: ____________________________________________

Where was questionnaire completed:  [ ] home  [ ] clinic  [ ] another centre

Comments: ________________________________________________

### Instructions:

QOL questionnaires should be filled out by the patient in the clinic when the patient comes for a scheduled visit. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. Patients will be asked to fill out the questionnaires as completely and accurately as possible. Since the patient may experience cognitive deterioration during treatment, a ‘significant other’ (e.g. a spouse) may help the patient complete the questionnaires, if the patient is unable to complete the form. The responder, identified in consultation with the patient and his/her physician will be recorded on the forms.

Date Completed:  ____ ____ __ - ____ ____ - ____ __

Please ensure this page is folded back before handing to the patient for questionnaire completion.

### CCTG use only

Logged: _______  Study Coord: _______  Res Assoc: _______

Data Ent’d: _______  Verif: _______

_____ - ___- ___  _____ - ___- ___  _____ - ___- ___  _____ - ___- ___
European Organization for Research and Treatment of Cancer (EORTC)

**Quality of Life Questionnaire (CE.7)**

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Do you have any trouble taking a long walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Do you have any trouble taking a short walk outside of the house?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Do you need to stay in a bed or a chair during the day?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Do you need help with eating, dressing, washing yourself or using the toilet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

**During the past week:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Were you limited in doing either your work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Were you short of breath?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Have you had pain?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Did you need to rest?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Have you had trouble sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Have you felt weak?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. Have you lacked appetite?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. Have you felt nauseated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. Have you vomited?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. Have you been constipated?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. Have you had diarrhea?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. Were you tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. Did pain interfere with your daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>21. Did you feel tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>22. Did you worry?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Did you feel irritable?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. Did you feel depressed?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. Have you had difficulty remembering things?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26. Has your physical condition or medical treatment interfered with your family life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27. Has your physical condition or medical treatment interfered with your social activities?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28. Has your physical condition or medical treatment caused you financial difficulties?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the following questions please circle the number between 1 and 7 that best applies to you.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>29. How would you rate your overall health during the past week?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Excellent</td>
</tr>
<tr>
<td>30. How would you rate your overall quality of life during the past week?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Excellent</td>
</tr>
</tbody>
</table>
Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

<table>
<thead>
<tr>
<th>Question</th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Did you feel uncertain about the future?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>32. Did you feel you had setbacks in your condition?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>33. Were you concerned about disruption of family life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>34. Did you have headaches?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>35. Did your outlook on the future worsen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>36. Did you have double vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>37. Was your vision blurred?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>38. Did you have difficulty reading because of your vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>39. Did you have seizures?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>40. Did you have weakness on one side of your body?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>41. Did you have trouble finding the right words to express yourself?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
During the past week:

<table>
<thead>
<tr>
<th></th>
<th>Not At All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
</tr>
</thead>
<tbody>
<tr>
<td>42. Did you have difficulty speaking?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>43. Did you have trouble communicating your thoughts?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>44. Did you feel drowsy during the daytime?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>45. Did you have trouble with your coordination?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>46. Did hair loss bother you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>47. Did itching of your skin bother you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>48. Did you have weakness of both legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>49. Did you feel unsteady on your feet?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>50. Did you have trouble controlling your bladder?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: ____________

Today's date (Year, Month, Day): ________________________________

Thank you.
APPENDIX VI - HEALTH UTILITIES ASSESSMENT

Introduction

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, disease free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making.
- They can be used as a weighting factor to adjust survival by quality of life.
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different diseases.
- Only utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations
- to evaluate the extent of change in health benefits of an individual, group, or population across time
- to evaluate new treatments, technologies, and patient management strategies
- to support approval of new drug applications or patient management strategies
- to try to provide the best value for health care dollars within and across diseases and health
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

Health utilities data are collected for research purposes, and will not be used for the patient’s individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.
The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient’s life, e.g. psychological distress, social disruption, symptoms, side-effects, et cetera.

The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment, as required by the schedule in the protocol (not required during treatment for this trial).

4. Assessments During Follow-up

The health utilities questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If...

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.
There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Four situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

D. The patient is no longer attending clinic during the scheduled follow-up period.

Should the patient no longer be attending clinic, he/she should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. In order to facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was received should be recorded on the questionnaire. The date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic.
6. **Inability to Complete Health Utilities Questionnaire (for reason other than illiteracy in English or French)**

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the EQ-5D assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.
Health Utilities Questionnaire – ENGLISH

CCTG Trial: CE.7

This page to be completed by the Clinical Research Associate

Patient Information
CCTG Patient Serial No: ____________  Patient Initials: ____ ____ ____
(first-middle-last)
Institution: ___________________________________________  Investigator: ______________________

Scheduled time to obtain assessment: please check (√)
☐ Prior to randomization

Off Treatment - prior to, or within 2 weeks of progression only:
☐ week 8  ☐ month 4  ☐ month 6  ☐ month 9  ☐ month 12  ☐ month 16  ☐ month 24
Then….  ☐ month 36  ☐ month 48  ☐ month 60  ☐ month ____

Were ALL questions answered?  ___ Yes  ___ No  If no, reason: ____________________________________________

Was assistance required?  ___ Yes  ___ No  If yes, reason: ____________________________________________

Where was questionnaire completed: ☐ home  ☐ clinic  ☐ another centre

Comments: ______________________________________________________________________________________
______________________________________________________________________________________________

Date Completed: __ __ __ __ - __ __ __ __

yyyy  mmm  dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _______  Study Coord: _______  Res Assoc: _______
Data Ent’d:  Verif:
______ - ______ - ______  ______ - ______ - ______  ______ - ______ - ______  ________  ________
EQ-5D-5L Questionnaire

CCTG: CE.7

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY
I have no problems in walking about  
I have slight problems in walking about  
I have moderate problems in walking about  
I have severe problems in walking about  
I am unable to walk about

SELF-CARE
I have no problems washing or dressing myself  
I have slight problems washing or dressing myself  
I have moderate problems washing or dressing myself  
I have severe problems washing or dressing myself  
I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
I have no problems doing my usual activities  
I have slight problems doing my usual activities  
I have moderate problems doing my usual activities  
I have severe problems doing my usual activities  
I am unable to do my usual activities

PAIN / DISCOMFORT
I have no pain or discomfort  
I have slight pain or discomfort  
I have moderate pain or discomfort  
I have severe pain or discomfort  
I have extreme pain or discomfort

ANXIETY / DEPRESSION
I am not anxious or depressed  
I am slightly anxious or depressed  
I am moderately anxious or depressed  
I am severely anxious or depressed  
I am extremely anxious or depressed
• We would like to know how good or bad your health is TODAY.

• This scale is numbered from 0 to 100.

• 100 means the best health you can imagine.
  0 means the worst health you can imagine.

• Mark an X on the scale to indicate how your health is TODAY.

• Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = 

Please check to make sure you have answered all questions.

Please fill in your initials to indicate that you have completed this questionnaire: ____________

Today's date (Year, Month, Day): ____________________________

Thank you.
APPENDIX VII - NEUROCOGNITIVE ASSESSMENT

Neurocognitive testing questionnaire booklets must be ordered by sites after local activation (see instructions under “Neurocognitive Assessment Ordering and Shipping below). These booklets contain test forms and instructions, to be utilized by certified examiners when administering cognitive tests.

The tests and battery format that will be done in this booklet includes the following and will take approximately 20 to 30 minutes to complete:

- **Memory** (5 minutes): Hopkins Verbal Learning Test (HVLT) (Brandt 1991).
- **Verbal Fluency** (5 minutes): Controlled Oral Word Association Test from the Multilingual Aphasia Examination (COWAT) (Benton and Hamsher 1978).
- **Visual Attention** (3 minutes): Trail Making Test A (Reitan 1958)
- **Executive Function** (5 minutes): Trail Making Test B (Reitan 1958)
- **Delayed Memory** (5 minutes): Recall and Recognition of Word List encoded from the HVLT (Brandt 1991).

Directions on administration and scoring of these tests is provided in the Administration Procedures for the Neurocognitive Test Battery in the section below.

Certification Procedures:

**Previously Credentialed:**
Members of site study teams previously credentialed to perform neurocognitive testing for any approved reciprocal study do not need to be re-certified for this study if that certification (or re-certification) occurred within the previous six months, or the examiner has done testing for that study in the past six months. Reciprocal studies typically include trials supervised by Dr. Cerhan or Dr. Jeffrey Wefel that use exactly the same test battery as CE.7. These include but are not limited to any of the following studies:

- BN001
- CC001
- CC003
- ECOG E3F05
- NCCTG N0577
- BN003
- BN005
- EF-25

Please note however, that site study teams **are required** to email documentation of the prior certification to the lead group. In this email be sure to include the name and number of the prior study, the approximate date of the certification and the CTEP site codes of all the institutions where the credentialing should be registered. The lead group will email notice of the certification to the CTSU Regulatory Office. The CTSU will list the certification on the CTSU Regulatory Support System (RSS). Study teams may check the status of their certification by logging into the CTSU website, clicking the blue ‘Regulatory’ tab then clicking the beige ‘Site Registration’ tab then entering the CTEP site code and protocol number in the search boxes and clicking ‘Go’.
Even for previously certified individuals, reviewing the details of this section, as well as the neurocognitive testing training video posted on the CTSU website is highly recommended. If several months pass between neuropsychological administrations, additional practice with volunteers is recommended.

**Not Previously Credentialed:**

Any individual member of a site study team who wishes to perform neurocognitive testing is required to be credentialed. Credentialing is specific to one individual person; it does not certify an entire study site or study team. If not previously credentialed, the study team member must follow this process:

Review the Administration Procedures for Neurocognitive Testing in this section of the protocol. Please have access to this document while you view the neurocognitive testing training videos posted on the CTSU website. Please allow enough time for the video to download. If you have difficulties downloading the video, please check with your institution’s computer support/help desk first before contacting the CTSU Help Desk.

Complete the “Neurocognitive Booklet for Certification Use Only.” The booklet includes a brief quiz and a practice test. Complete the practice test with a colleague (not a patient).

Scan and email a copy of the **entire booklet** to Dr. Butts at AButts@mcw.edu. If unable to email, the booklet may instead be mailed to Dr. Butts at:

Dr. Alissa Butts  
Medical College of Wisconsin  
Neuropsychology – Elizabeth Bogadi  
8701 Watertown Plank Rd.  
Milwaukee, WI 53226

If mailing the booklet, remember to keep a copy on site. Email is the most efficient path to certification.

If there are concerns, Dr. Butts will email or call the member of the site study team to review. If there are no concerns, she will confirm the site study team member’s certification by email. The site should then submit the Certification Confirmation email to the CTSU per Section 6.1.1. The CTSU will list the certification on the CTSU Regulatory Support System (RSS). Study teams may check the status of their certification by logging into the CTSU website, clicking the blue ‘Regulatory’ tab then clicking the beige ‘Site Registration’ tab then entering the CTEP site code and protocol number in the search boxes and clicking ‘Go’.

If there are questions about testing procedures, please contact the Study Coordinator for the trial.

Credentialing does not expire. However, if a number of months go by between testing patients, please ensure readiness to test by reviewing the Administration Procedures for Neurocognitive Testing in the protocol and/or viewing the training video posted on the CTSU website and/or performing practice testing with a colleague.
Neurocognitive Assessment Ordering and Shipping:

Ordering of Neurocognitive Certification and Patient Neurocognitive Testing Booklets

The study site should obtain all necessary neurocognitive certification and neurocognitive patient testing questionnaire booklets before pre-registering patients. Booklets should be ordered from CTSU by completing the CTSU Supply Request Form on the CTSU website. Note: CTSU will not send questionnaire booklets until the site has submitted a copy of their IRB approval excerpt to the CTSU Regulatory Office. Neurocognitive certification and neurocognitive patient testing questionnaire booklets must be used; copies are not acceptable for submission.

Timing of Neurocognitive Testing

Baseline neurocognitive testing will be performed before cranial radiation (SRS or WBRT) is initiated and thereafter as outlined in Section 5.0 of the protocol.

Neurocognitive Tests Format

The credentialed site study team member will administer the neurocognitive tests to the patient using the patient questionnaire titled “Neurocognitive Examiners Booklet”. There are six different versions of the questionnaires labeled form 1, form 2, form 3, form 4, form 5 and form 6. Each questionnaire has a unique version of the Hopkins Verbal Learning Test (HVLT) to prevent patient recall from a prior test. The questionnaire booklet requires approximately 20 to 30 minutes to complete and includes the following tests:

- **Memory**: Hopkins Verbal Learning Test (HVLT)
- **Fluency**: Controlled Oral Word Association Test from the Multilingual Aphasia Examination (COWAT)
- **Visual Attention**: Trail Making Test A
- **Executive Function**: Trail Making Test B
- **Delayed Memory**: Recall and Recognition of Word List encoded from the HVLT

Examiners should print the Administration Procedures for Neurocognitive Test Battery instructions below and have them available as a reference.

Submission of the Completed Neurocognitive Test Questionnaires

Completed test forms must be signed by the credentialed site study team member administering the neurocognitive tests. Be sure to include the patient’s initials and study ID number on the Neurocognitive Booklet. Retain a copy of the completed neurocognitive booklet at the treating institution.

Please send originals of the completed patient test questionnaires directly to CCTG, attention Chad Winch:

Queens University - CCTG
10 Stuart Street
Kingston, Ontario
Canada
K7L 3N6

Copies of the test booklets must also be kept on file at the site. Completed test booklets should be mailed to CCTG as soon as possible to ensure that the quality control review can be done in a timely manner.
Quality Control for Patient Neurocognitive Testing Booklets

Throughout the study, Dr. Butts will review all patient questionnaire booklets for quality control purposes. Procedural deviations will be identified and the site study team member performing the neurocognitive testing will be notified of the results of the review as needed. If significant procedural variations are noted, re-training of the test administrator will be required. Completed patient questionnaire booklets should be mailed to CCTG as soon as possible to ensure that the quality control review can be done in a timely manner.

Administration Procedures for the Neurocognitive Test Battery:

1. Testing should 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. On follow-up visits, it is preferred that patients complete the neurocognitive test battery before seeing the physician since the emotional impact of the results of their follow-up brain scan may influence the patient’s performance on the neurocognitive assessments.

2. Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. These versions will be alternated in the testing booklets provided. Always try to use the correct booklet labeled for the patient’s visit number (this number is identified on the title page of each booklet).

3. You may fill the delay interval between COWA and HVLT-R Part B (Delayed Recall) with QOL questionnaires.

4. Originals of the test booklets should be mailed to CCTG, attention Chad Winch:
   Queens University - CCTG
   10 Stuart Street
   Kingston, Ontario
   Canada
   K7L 3N6

5. Please keep copies of all completed original test booklets. In the event of questions regarding testing procedures, contact Dr. Butts at the telephone number and email address listed on the Protocol Resources page of the protocol.

6. Patients should never be given copies of their tests to avoid learning the material between test administrations.

Setting up for Neuropsychological Testing:

- Private room
- Door that closes
- Quiet
- Alone with just the patient - No family members
- May want to hang a sign that says “do not disturb”
- Some tests are timed – it is very important not to be interrupted
- Desk for you both to write on (clipboard works in a pinch)
- Stopwatch, do not try to time using a wall clock or regular watch.
- Black ink pens (one for you and one for the patient)
Testing Tips:

- Do not indicate to the patient how well they are doing.
- Hide your writing from the patient so they cannot get feedback on how they are performing.
- However, it is OK to be generically encouraging (make sure you make the same response whether patient is performing well or not).
- Please do not assist them in any way if they struggle with a task; we need an accurate view of what they can do themselves.
Test Instructions
Administer the tests in the following order to every patient at every visit

1. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)
   This test has three parts and six alternate forms:
   
   1. Part A – Learning Trials: Complete the three learning trials first
   2. Part B - Delayed Recall: Complete after a 20-minute delay that includes administration of Trail Making Tests and COWA.
   3. Part C - Delayed Recognition: Complete immediately after Delayed Recall

Part A – Learning Trials: Trial 1

Examiner: “I am going to read a list of words to you. Listen carefully, because when I am through, I’d like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?”
   
   • Read the words at the rate of one word every 2 seconds. (Practice reading words at this rate, as it is critical not to go faster or slower as it impacts task difficulty and thus comparability with previous or future exams.)
   
   Examiner: “OK. Now tell me as many of those words as you can remember.”
   
   • Check off the words the patient recalls on the form.
   • If a word is said that is not in the list (for example, “intrusion”), do not write that word on the form and say nothing to the patient about the word not being on the list.
   • There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
   • If not, move on to trial 2.
   • Never tell the patient whether a word is correct, and don’t tell them how many words are left on the list (e.g., don’t say “there are three more.”).

Part A – Learning Trials: Trial 2

Examiner: “Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time.”
   
   • Read the words at the rate of one word every 2 seconds.
   • Check off the words the patient recalls on the form.
   • If a word is said that is not in the list (for example, “intrusion”), do not write that word on the form and say nothing to the patient about the word not being on the list.
   • There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
   • If not, move on to trial 3.
Part A – Learning Trials: Trial 3

Examiner: “I am going to read the list one more time. As before, I’d like you to tell me as many of the words as you can remember, in any order, including all the words you’ve already told me.”

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (for example, “intrusion”), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- Do not tell the respondent that recall of the words will be tested later.
- Record the time on the clock that you complete ‘Part A – Free Recall’ (for example, 10:00 am) on the designated space on the HVLT-R form.

2. TRAIL MAKING TEST [Timed Test]

Part A – Sample: The Sample for Part A must be completed/attempted by each patient at 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 black pen 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 and indicate the corresponding reason on the Trail Making A & B Scoring (TMABS) sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

**Part A – Test:** 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.**”

- 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.
- 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. Complete the Trail Making A & B Scoring (TMABS) sheet indicating the reason the test was terminated and the last correct number reached on the test.
- If the patient successfully completes the test, record the time to completion on the Trail Making A & B Scoring (TMABS) sheet 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 at 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 A & B Scoring (TMABS) sheet. If the patient completes Sample B correctly and appears to understand what to do, proceed immediately to Part B.

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.
- The patient must complete the test in 5 minutes or less.
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED “END.”
- Record the time to completion on the Trail Making A & B Scoring (TMABS) 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. Complete the Trail Making A & B Scoring (TMABS) sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.
- If the patient successfully completes the test, record the time to completion on the Trail Making A & B Scoring (TMABS) sheet in minutes and seconds.

3. CONTROLLED ORAL WORD ASSOCIATION (COWA) [Timed Test]
This test has three parts (letters).

Examiner: “I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say ‘Rochester’ or ‘Robert’. Also, do not use the same word again with a different ending, such as ‘Eat,’ and ‘Eating.’
“For example, if I say ‘s,’ you could say ‘son,’ ‘sit,’ ‘shoe,’ or ‘slow.’ Can you think of other words beginning with the letter ‘s?’”

Wait for the patient to give a word. If it is a correct response, say “good”, and ask for another word beginning with the letter “s.” If a second appropriate word is given, proceed to the test itself.

If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.

If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring sheet.

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

Examiner: “That is fine. Now I am going to give you another letter and again you say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP.”

“You will have a minute for each letter. The first letter is ‘___’ (see scoring sheet).

Allow exactly one minute for each letter

- If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., “Tell me all the words you can think of that begin with a “c”).
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing one minute for each.

Recording and Scoring:

- The COWA provides lines on which the patient’s responses can be entered (e.g., write in the word that is said by the patient). If his/her speed of word production is too fast to permit verbatim recording, a “+” should be entered to indicate a correct response.
- Incorrect responses should be struck through with a line. It is usually easiest to record each response and incorrect responses can be crossed out later during scoring.
- If the patient provides more responses than there are lines on the record sheet, place check marks in the boxes to indicate correct responses only. Count all the correct responses. The number of correct words should be indicated below each column.

Comments on scoring:

- Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.
- The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word (e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs) are not considered correct responses.
• Patients often give both a verb and a word derived from the verb or adjective (e.g., fun-funny; sad-sadness). These are not considered correct responses. On the other hand, if the word refers to a specific object (e.g., foot-footstool; hang-hanger), it would be counted as a correct answer.

• Many words have two or more meanings (e.g., foot; can; catch; hand). A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.

• Slang terms are OK if they are in general use.

• Foreign words can be counted as correct if they can be considered part of the lexicon (for example, pasta; passé; lasagna), the criterion being their listing in a standard dictionary. All incorrect and repeated responses MUST be crossed out with one single line. Additionally, all duplicate entries that have been verified to have different meanings must be marked “ok” Refer to the descriptions above for guidelines for acceptability. Add the total number of correct responses in each column and input the totals where indicated on the COWA worksheet.

• If the test is discontinued or omitted, please mark this on the bottom of the test form.

HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

Part B – Delayed Recall

DO NOT READ THE WORD LIST AGAIN.

Record the time on the clock that you start ‘Part B – Delayed Recall’ (for example, 10:20 am) on the designated space on the HVLT-R form.

Administer ‘Part B – Delayed Recall’ after completing all Trail Making Tests and the COWA.

There should be at least 20 minutes between ‘Part A’ and ‘Part B’ of the HVLTR. If the time is too short, allow the patients to complete a questionnaire.

Examiner: “Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember.”

• Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.

• If a word is said that is not in the list (for example, “intrusion”), do not write that word on the form and say nothing to the patient about the word not being on the list.

• There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.

• If not, record the number of words that were correctly recalled on the summary form.

Part C – Delayed Recognition

Examiner: “Now I’m going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I’d like you to say “Yes” if it was on the original list or “No” if it was not. Was [word] on the list?”

• Read the words from the top of the columns down.

• Check either the “Y” (Yes) or “N” (No) box next to each word to indicate the patient’s response.
Guessing is allowed.

If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason.

The score for this portion of the HVLT-R is the number of list words (i.e., words that in CAPS) correctly identified (“yes” response) minus the number of non-list words (i.e., words in lower case) incorrectly identified (“yes” response). Therefore, the actual score can range from −12 (no list words identified and all non-list words identified) to +12 (all list words identified and no non-list words identified).

Remote Administration of Neurocognitive Tests:

Compliance with the trial protocol should be ensured to every extent possible, however in emergency situations, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of patients are permissible.

In these rare circumstances, when in person testing is not feasible, CCTG is permitting alternate methods of assessment for the neurocognitive administration. This includes the use of telephone contact, virtual visit, or alternative locations for assessment for the administration procedures of the Neurocognitive Test Battery. These minor deviations to the protocol must be reported to CCTG (e.g. in Electronic Data Capture (EDC) or using trial specific deviation logs as directed by CCTG) within 4 weeks of the end of the Emergency Situation, unless otherwise instructed by CCTG, and to your REB at the next amendment or annual approval. (Please see Appendix X for details.)

If the neurocognitive assessments are to be administered remotely, the test instructions for administration of the HVLT-R and COWA outlined above should still be used [Callum 2014]. However, instead of using the Written Trail Making Test in item #2 above, the Oral Trail Making Test (Oral TMT) should be substituted [Ricker 1996; Mrazik 2010].

Oral Trail Making Test

Prior to remote administration of the HVLT-R and COWA, as well as remote administration of the Oral TMT, neurocognitive examiners must complete the required additional training. Training required includes review of the Remote Testing and Oral TMT Administration slides, and completion of the Post-Training Quiz (all available on the trial website). After viewing the training slides and completing the quiz, sites must download, complete, sign, and submit the Confirmation of Completion Attestation Form to CTSU. Relevant materials for the Oral TMT are available on the trial website.

Sites are encouraged to contact Dr. Alissa Butts prior to their first remote administration of the neurocognitive testing, even after having completed online training, and should they have any additional questions regarding remote administration of any neurocognitive tests, including administration or scoring of the Oral TMT.

Completion of the Oral TMT training is not required for participation in the trial, or for local activation purposes, but must be completed prior to any remote administration of neurocognitive assessments. As such, we encourage sites to proactively complete the training for Oral TMT if it appears their institution is entering into an emergency situation where in-person examining will not be feasible or safe.
Administration Procedures for the Oral Trail Making Test (TMT):

Remote testing may be administered by telephone (preferred), or videoconference ONLY when in-person testing is not possible, and in emergency situations.

If remote administration is required, please clearly write at the top of the front page of the neurocognitive booklet “REMOTE ADMINISTRATION – Telephone” or “REMOTE ADMINISTRATION – Videoconference”, and include this information in EDC. Administer the tests in the same order as described in the Test Instructions section above for every patient. However, please substitute the Oral TMT for the Written TMT.

Materials needed for remote neurocognitive administration will include:

- The standard Neurocognitive Testing Booklet
- Quality of Life AND Health Utilities Index Questionnaires (i.e. QLQ-C30 + BN20, EQ-5D-5L)
- Administration and Scoring Sheet for the Oral TMT
- Post Remote Testing Validity Checklist

The Oral Trail Making Test should replace the Written Trail Making Test for remote assessment. In order to ensure that the 20 minute delay between Parts A and B of the HVLT-R test are achieved (i.e. Delayed Recall), it is recommended that the patient completes some or all of the trial questionnaires to fill the time.

Upon completion of remote neurocognitive testing, the examiner should then complete the Post Remote Testing Validity Checklist. Please submit the completed neurocognitive booklet, the completed Oral TMT forms, and the validity checklist to CCTG as a package. Please ensure patient ID is included on the forms.

Oral Trail Making Test Instructions:

Oral Trail Making Test Part A
1. “I would like you to count from 1 to 25 as quickly as you can – 1, 2, 3, and so on. Are you ready? Begin.”
2. Start your stopwatch when the instruction is given to “begin”. Stop timing when subject reaches #25
3. When errors are made on Part A, reorient them to the last correct number by saying, “You said ‘[specific number],’ please continue from there.”

Scoring:
- Did the patient reach the end of the test within the 3 minute time limit?
- Record Time (seconds) when the patient reaches #25, or the last number reached by the time limit.
- Record the number of errors
- Submit the Administration and Scoring sheet to CCTG, along with the completed neurocognitive test booklet. Please also complete and submit the Post Remote Testing Validity Check Sheet with the package.
Oral Trail Making Test Part B

1. “Now I would like you to count again, but this time you are to switch between number and letter, so you would say 1-A-2-B-3-C, and so on, until I say ‘stop’. Are you ready? Begin.”
2. Start your stopwatch when the instruction is given to “begin”. Stop timing when the subject reaches #13.
3. When errors are made on Part B, reorient them to the last correct pair by saying: “You said ‘[specific number] [specific letter]’;’ Continue from there.”

Keep the stopwatch running during any corrections, as is written in TMT. For part B, timing is discontinued once subjects reach the number 13, identical to instructions for WTMT.

Scoring:
- Did the patient reach the end of the test within the 5 minute time limit?
- Record Time (seconds) when the patient reaches #13, or the last number/letter reached by the time limit.
- Record the number of errors
- Submit the Administration and Scoring sheet to CCTG, along with the completed neurocognitive test booklet. Please also complete and submit the Post Remote Testing Validity Check Sheet with the package.
The 7th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org). These staging criteria should be used for new trials.
APPENDIX IX - RECOMMENDED IMAGING PROTOCOLS

Recommended 1.5T Protocol

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Recommended 3T Protocol

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<td>90°/180°</td>
<td>90°/≥ 160°</td>
<td>10°-15°</td>
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<td>≥256</td>
<td>≥256</td>
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<td>≥1</td>
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</tr>
<tr>
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<td>Up to 2x</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
<td>Up to 2x</td>
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</table>

(references: Ellingson 2015; Kaufmann 2020)
APPENDIX X - EMERGENCY SITUATIONS AND COMPLIANCE

Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial as well as any associated sub-studies should be ensured to every extent possible, should be ensured to every extent possible, however in emergency situations, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of patients are permissible.

In these rare circumstances, minor deviations that do not impact patient safety or willingness to participate or trial integrity, which have been justified and documented in the medical record by the QI/SI will not be considered to be REB reportable deficiencies requiring action, but must be reported to CCTG (e.g. in Electronic Data Capture (EDC) or using trial specific deviation logs as directed by CCTG) within 4 weeks of the end of the Emergency Situation, unless otherwise instructed by CCTG, and to your REB at the next amendment or annual approval.

Centres should also discuss these reporting requirements with their local REB, and review the trial website for additional guidance specific to the trial.

Minor Protocol Deviations:

- Missed or delayed protocol mandated visits or investigations on treatment or in follow up.
- Changes in study drug distribution (e.g. drug distributed remotely or IV drug given at satellite site), providing permitted by local SOPs, or written procedure established and is approved by CCTG or acceptable per further instruction from CCTG. Note there will be no exceptions for injectable/IV investigational agents as must be administered at participating site.
- Alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location for assessment).
- Patient care and evaluations provided by non-research staff, providing overseen by QI/SI who must make all treatment decisions and ensure that all required information and results will be reported to allow central data submission. Includes physical exam, clinical laboratory tests, research blood collections that can be shipped centrally, imaging, non-investigational drug therapy*, standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing*.
  
  *Must be approved by CCTG or acceptable per further instruction from CCTG.

- Re-treatment following extended treatment delays if protocol specifies that excessive delays require discontinuation, providing other protocol requirements for discontinuation have not been met and either discussed with CCTG or acceptable per further instruction from CCTG.

Note:

- Applicable only to COVID-19 and other CCTG designated emergency situations.
- No waivers will be given for eligibility, including performance of protocol mandated tests/imaging.
- Deficiencies will be issued if patients are enrolled when trial is on accrual hold, for unreported Serious Adverse Events as well as changes in drug distribution/administration and/or re-treatment after extended treatment delays when not discussed and approved by CCTG or acceptable per further instruction from CCTG.
- Deviations or changes that are believed to impact patient safety, compromise the study integrity or affect willingness to participate are still considered Major Protocol Violations and must be reported to CCTG and your REB. These include more than a minimal delay in protocol therapy administration.
LIST OF CONTACTS

For all sites:

<table>
<thead>
<tr>
<th>Contact</th>
<th>Tel. #</th>
<th>Fax #</th>
</tr>
</thead>
</table>
| ELIGIBILITY CHECKLIST | Sue Casey  
Clinical Trials Assistant, CCTG  
Email: scasey@ctg.queensu.ca | 613-533-6430 | 613-533-2941 |
| STUDY SUPPLIES | Available on CCTG Website:  
http://www.ctg.queensu.ca  
under: Clinical Trials |  |  |
| PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES | Chad Winch  
Study Coordinator, CCTG  
Email: cwinch@ctg.queensu.ca | 613-533-6430 | 613-533-2941 |
|  |  
or:  
Dr. Chris O’Callaghan  
Senior Investigator, CCTG  
Email: cocallaghan@ctg.queensu.ca |  |  |
| STUDY CO-CHAIRS | Dr. David Roberge  
Study Co-Chair  
Email: david.roberge.chum@ssss.gouv.qc.ca  
or  
Dr. Michael Chan  
Study Co-Chair  
Email: mchan@wakehealth.edu |  |  |
| SERIOUS ADVERSE EVENT REPORTING | Chad Winch  
Study Coordinator, CCTG  
Email: cwinch@ctg.queensu.ca | 613-533-6430 | 613-533-2941 |
Additional US contact information:

<table>
<thead>
<tr>
<th>CONTACT INFORMATION</th>
<th>For regulatory requirements:</th>
<th>For patient enrollments:</th>
<th>For study data submission:</th>
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</thead>
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<tr>
<td>Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at <a href="https://www.ctsu.org/">https://www.ctsu.org/</a>, and select the Regulatory Submission sub-tab under the Regulatory tab.)</td>
<td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at <a href="https://www.ctsu.org/OPEN_SYSTEM/">https://www.ctsu.org/OPEN_SYSTEM/</a> or <a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a>.</td>
<td>Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.</td>
<td></td>
</tr>
<tr>
<td>Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or <a href="mailto:CTSURegHelp@coccg.org">CTSURegHelp@coccg.org</a> to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.</td>
<td>Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</td>
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</tbody>
</table>

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at [https://www.ctsu.org](https://www.ctsu.org). Access to the CTSU members’ website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

Institutions will order the following supplies from the CTSU Operations Office: *Neurocognitive Booklets.* Supplies can be ordered by downloading and completing the CTSU Supply Request Form (available on the protocol-specific page on the CTSU website) and submitting it as instructed on the form.

**For clinical questions (i.e. patient eligibility or treatment-related):**
See Contacts page above this table

**For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)** contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

**The CTSU Website is located at [https://www.ctsu.org](https://www.ctsu.org).**