NRG ONCOLOGY

NRG-BN001
ClinicalTrials.gov NCT02179086.

RANDOMIZED PHASE II TRIAL OF HYPOFRACTIONATED DOSE-ESCALATED PHOTON IMRT OR PROTON BEAM THERAPY VERSUS CONVENTIONAL PHOTON IRRADIATION WITH CONCOMITANT AND ADJUVANT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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 NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Medical Research Foundation, Inc., and SWOG. (8/7/15)

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NRG ONCOLOGY

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RANDOMIZED PHASE II TRIAL OF HYPOFRACTIONATED DOSE-ESCALATED PHOTON IMRT OR PROTON BEAM THERAPY VERSUS CONVENTIONAL PHOTON IRRADIATION WITH CONCOMITANT AND ADJUVANT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

Protocol Agent

Agent	Supply	NSC #	IND #
Temozolomide	Commercial	N/A	Exempt

Participating Sites

☐ U.S. Only
☐ Canada Only
☒ U.S. and Canada
☐ Approved International Member Sites

Document History

	Version/Update Date	Broadcast Date
Amendment 2	**February 16, 2017**	April 25, 2017
Amendment 1	August 7, 2015	September 14, 2015
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NRG Oncology
1-800-227-5463, ext. 4189

CTSU CONTACT INFORMATION (2/16/17)		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at 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.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization		
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.		

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NRG ONCOLOGY

NRG-BN001

Randomized Phase II Trial of Hypofractionated Dose-Escalated Photon IMRT or Proton Beam Therapy Versus Conventional Photon Irradiation With Concomitant and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma

SCHEMA (2/16/17)

Group I: Photon IMRT Centers *Proton Centers: Please see schema on next page.*

Closed to accrual for all sites 12/20/16.
Reopened to accrual for credentialed advanced imaging sites with Amendment 2.

STEP 1 REGISTRATION
Central Pathology Review for confirmation of histology and adequacy of tissue for MGMT analysis
NOTE: Tumor tissue must be received and central review confirmation completed before STEP 2 registration can occur.

↓

STEP 2 REGISTRATION

STRATIFY
RPA Class: III, IV, or V
MGMT Status: Methylated, Unmethylated, or Indeterminate

RANDOMIZE*

↓ ↓

Arm A1: Reference Arm
Photon irradiation using 3DCRT or IMRT:
46 Gy in 23 fractions followed by a sequential boost for an additional 7 fractions to 60 Gy
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles

Arm B: Experimental Arm
Photon dose-intensified irradiation using IMRT:
50 Gy in 30 fractions with a simultaneous integrated boost to 75 Gy in 30 fractions.
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles

*Randomization is 1:2 in favor of the experimental arm.

See Section 5.0 for credentialing requirements, Section 6.0 for radiation therapy details, and Section 7.0 for drug therapy details.

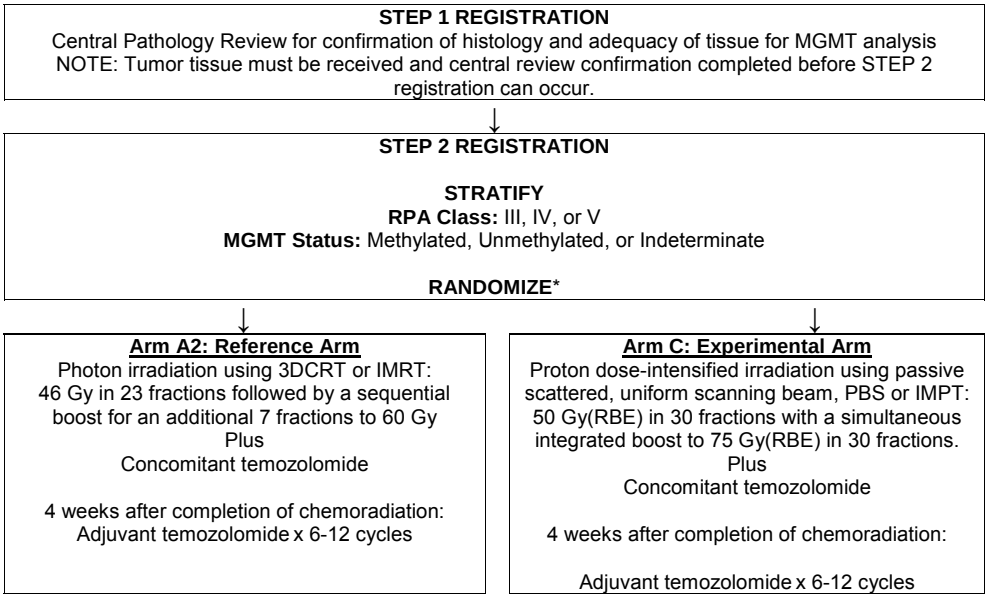
Photon IMRT centers that enroll patients in Group I, but subsequently develop the capability to deliver proton therapy, can transition to enrolling patients in Group II (see schema on next page) if the proton therapy treatment modality to be used has been approved by the IROC Houston QA Center and other credentialing procedures described in Section 5.1 have been met. However, once the center enrolls patients in Group II (as a proton center), the center can no longer enroll patients in Group I (as a photon IMRT center).

Photon IMRT centers that currently enroll patients in Group I, but would like to partner with proton centers, can transition to enrolling patients in Group II after the partnership is established. However, once the center starts enrolling patients in Group II (as a proton center), the center can no longer enroll patients in Group I (as a photon IMRT center). The enrolling center should establish an agreement with the proton center regarding roles and responsibilities so all data submission is accounted for, and would still be responsible for the cases randomized to the proton arm. While there is no formal documentation required of NRG for this agreement, the proton center staff who would submit the digital RT data (TRIAD site user role) and who would participate in care for the patient at the proton center must be on the CTSU site roster of the enrolling center.

Group II: Proton Centers

All proton centers must be able to deliver photon therapy or partner with a photon therapy site for patients randomized to Arm A2. It is recommended that proton sites not able to deliver photon therapy discuss logistics for a treatment partnership with partnering sites prior to registering patients, See the beginning of Section 12 for data submission logistics pertinent to this partnership.

NOTE: IF YOUR SITE IS CREDENTIALED FOR PROTONS FOR THIS TRIAL YOU **MUST** REGISTER TO GROUP II ONLY.



*Randomization is 1:2 in favor of the experimental arm.

See Section 5.0 for credentialing requirements, Section 6.0 for radiation therapy details, and Section 7.0 for drug therapy details.

Patient Population: (See Section 3.0 for Eligibility)

- Histologically proven diagnosis of glioblastoma (WHO grade IV) **confirmed by central review** prior to step 2 registration.
- Tumor tissue that is **determined by central pathology review** prior to step 2 registration to be of sufficient quantity for central analysis of MGMT status.
- The tumor must be located in the supratentorial compartment only (any component involving the brain stem or cerebellum is not allowed).

Required Sample Size: 606 randomized patients (318 Group I, 288 Group II)
(Based on cases entered on STEP 2 registration)

1.0 INTRODUCTION

Glioblastoma (GBM) is the most common primary malignant brain tumor. Despite surgery, conventional radiotherapy, and chemotherapy, the median survival for GBM remains poor at approximately 15-16 months in contemporary series (Grossman, Ye et al. 2010, Gilbert, Wang et al. 2011). Although adjuvant chemoradiotherapy has been shown to increase survival, the predominant pattern of failure remains local (Chan, Lee et al. 2002, Milano, Okunieff et al. 2010). This may be due in part to the widespread hypoxia present in the microenvironment of GBM. These hypoxic niches are associated with release of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) (Rong Y., 2006). Hypoxic niches within the tumor are also believed to harbor stem cells that resist treatment and are putatively responsible for tumor regrowth (Seidel, S., 2010). Radiation treatment of GBM and other solid tumors is likely hampered by decreased biologic effectiveness due to treatment-resistant clones in regions of hypoxia.

Intensification of local therapy, through concomitant escalation of radiotherapy dose and dose-per-fraction is an emerging approach to overcome hypoxia-related treatment resistance. Prior dose escalation studies with radiotherapy alone suggest that the pattern of failure can be altered and local control improved with radiotherapy dose escalation (Nakagawa, Aoki et al. 1998, Fitzek, Thornton et al. 1999, Tanaka, Ino et al. 2005). Though prior studies of focal radiotherapy boost techniques such as radiosurgery and brachytherapy have failed to show a survival benefit, the impact of local therapy intensification has not been addressed in the context of concomitant temozolomide, a radiotherapy sensitizer and chemotherapeutic agent which has demonstrated improved survival when delivered with radiotherapy.

Contemporary trials have shown that high radiotherapy doses (approximately 80 Gy) with concomitant and adjuvant temozolomide can be safely delivered (Mizoe, Tsujii et al. 2007, Tsien, Brown et al. 2012). Although higher doses of up to 90 Gy have been evaluated in small series of patients treated with proton therapy, the safety of this dose level with temozolomide has not been demonstrated. Thus, we propose to investigate whether radiotherapy dose intensification, to levels safely tested in the phase I context with temozolomide, i.e less than 80 Gy, on the backbone of radiosensitizing temozolomide chemotherapy overcomes hypoxia-related treatment resistance and augments local control and thereby survival.

1.1 Conventional Chemoradiation

Standard radiotherapy currently employs a total dose of 60 Gy in 30 fractions. This is based on historical dose-response analyses in the pre-temozolomide era. Walker et al. (Walker, Strike et al. 1979) reported on 420 patients treated on Brain Tumor Cooperative Group protocols and observed significant improvement in median survival from 28 to 42 weeks in the patients treated with doses of 50-60 Gy, compared to lower doses. Similarly, a Medical Research Council study of 443 patients also showed a significant survival advantage (median survival 12 vs. 9 months) in patients who received 60 Gy compared to those who received 45 Gy (Bleehen and Stenning 1991). A legacy phase III trial escalating dose from 60 to 70 Gy in conventional 2-Gy fractions in the pre-temozolomide era observed no further survival benefit (Nelson et al. 1988).

The vast majority of the radiotherapy dose-escalation studies have been conducted in the pre-temozolomide era. Temozolomide is an oral alkylating agent with demonstrated clinical antitumor activity against malignant gliomas, especially when delivered concomitantly with radiotherapy. The definitive EORTC phase III trial established that the addition of concomitant and adjuvant temozolomide to conventional radiotherapy (60 Gy in 30 fractions) increased the median survival of patients with GBM from 12.1 to 14.6 months without a substantial increase in toxicity (Stupp, Mason et al. 2005). A recent update from this trial demonstrated a 10% 5-year survival benefit, providing additional evidence of the efficacy of this regimen (Stupp, Hegi et al. 2009). This chemoradiotherapy regimen has become the backbone of standard postoperative treatment for patients with GBM but has never adequately been tested in a radiotherapy dose-escalation or intensification context.

1.2 Local Therapy Intensification

With this standard postoperative chemoradiotherapy regimen, the predominant pattern of failure remains local, highlighting the importance of investigating more intensive local therapies. Photon IMRT and proton beam therapy represent novel radiotherapy approaches to intensifying local therapy. Given their highly conformal dose distribution and ability to spare adjacent normal structures, including normal brain parenchyma, higher total doses can be delivered safely. In addition to escalating physical dose, both modalities also enable the delivery of higher biologically effective doses, through higher dose-per-fraction delivery using a simultaneous integrated boost technique. Thus, we propose to investigate the potential effectiveness of intensifying local therapy with concomitant dose and dose-per-fraction escalation using photon IMRT or proton beam therapy strategies for patients with GBM.

1.3 Dose-Escalation Clinical Trials Without Temozolomide

RTOG 9803 was a phase I trial to evaluate the feasibility and toxicity of dose-escalated photon radiotherapy concurrent with BCNU chemotherapy in patients with supratentorial GBM (Tsien, C., J. Moughan, et al. 2009). 209 patients were enrolled and stratified into two groups based on size of planned target volume (<75cc vs. ≥75cc). Within each stratum, four radiotherapy dose levels were evaluated: 64, 72, 78 and 84 Gy; all treatments were delivered with a fraction size of 2 Gy. Acute and late grade ≥3 radiotherapy-related toxicities were no more frequent at higher radiotherapy doses or with larger tumors. No dose-limiting toxicities were observed at any dose level in either stratum, and as a result dose was escalated to 84 Gy in both strata. Median time to radiotherapy-related necrosis was 8.8 months (range 5.1-12.5 months). This study therefore demonstrated the feasibility and tolerability of photon dose escalation with an acceptable risk of late CNS toxicity, including at doses as high as 84 Gy (all delivered at 2 Gy per fraction, with no dose-per-fraction intensification). However, this study was conducted with concurrent BCNU chemotherapy, not the current standard approach of concurrent and adjuvant temozolomide.

1.4 Dose-Escalation Clinical Trials With Temozolomide

Recently, Tsien et al. published results of a clinical trial that escalated dose **and** dose-per-fraction from 66 to 81 Gy in 30 fractions during chemoradiotherapy with temozolomide for patients with GBM (Tsien, Brown et al. 2012). The maximum tolerated dose with concurrent temozolomide was 75 Gy in 30 fractions (2.5 Gy per fraction). Median survival was 20.1 months, suggesting improved efficacy comparable to other contemporary studies. Interestingly, the probability of in-field failure decreased with increasing dose escalation. Additionally, due to safety concerns, this study was restricted to patients with a maximal diameter of postoperative contrast-enhancing tumor of 5 cm. Given the demonstrated feasibility, safety, and promising results, this approach to dose escalation and intensification (including its tumor size limitation) has been selected for this protocol.

1.5 Potential Benefit of Proton Beam Therapy Versus Photon IMRT

1.5.1 Toxicity/Symptom Burden

An important limitation to hypofractionation is late radiation toxicity, such as symptomatic radiation necrosis or leukoencephalopathy (Reddy, Damek et al. 2012). These adverse effects arise from high dose-per-fraction irradiation of adjacent normal brain parenchyma and can be minimized with highly conformal dose delivery.

In contrast to the typical photon dose deposition characteristics, proton therapy is characterized by lower dose within the entry path of the beam and the steep dose distribution referred to as the Bragg peak that can be deposited directly into the defined target volume. The steep dose fall-off in the beam exit path provides for better sparing of normal tissue (ICRU 2007). These physical advantages enable increased normal tissue sparing and thereby presumably safer delivery of higher doses to the defined target volume.

Conducted in the pre-temozolomide era, prior studies of proton beam therapy have demonstrated the requisite conformality and associated safety profile for dose escalation up to 90 GyE or higher in patients with newly diagnosed GBM using conventional fractionation (fraction size of 2 Gy or

less). Mizumoto et al. (Mizumoto, Tsuboi et al. 2010) reported on a phase I/II study of 20 patients with supratentorial GBM treated with mixed proton/photon irradiation to 96.6 GyE in 56 twice-daily fractions with concomitant nimustine chemotherapy. Median survival was 22 months. Importantly, late radiation necrosis was observed in only 1 patient, and late leukoencephalopathy was noted in a second patient. Similar results have been reported by Fitzek et al. (Fitzek, Thornton et al. 1999), who observed a median survival of 20 months after treating newly diagnosed GBM to 90 GyE. Interestingly, only 1 recurrence was observed in regions treated to 90 GyE.

This study seeks to escalate dose and dose-per-fraction with concurrent and adjuvant temozolomide to the maximum tolerated dose established by the aforementioned University of Michigan study (Tsien, Brown et al. 2012). In that study, the maximum tolerated dose of 75 Gy in 30 fractions was associated with a 14% probability of dose-limiting toxicity with the use of photon IMRT. Given its steep dose fall-off, narrow penumbrae, and reduced integral dose, proton beam therapy may permit safer dose escalation/intensification.

1.5.2 Preservation of the CD4 Lymphocytic Compartment and Improved Therapeutic Efficacy

Emerging data suggest that in the setting of postoperative radiotherapy for malignant gliomas, the circulating lymphocyte compartment putatively represents a biologically relevant normal tissue compartment. Initial observations of newly diagnosed high-grade glioma patients treated in the pre-temozolomide era with radiotherapy have demonstrated a significant reduction in CD4 counts over the course of treatment. Specifically, after 6 weeks of radiotherapy, 47% of patients had CD4 counts <300 cells/mm^3 and 26% had CD4 counts <200 cells/mm^3 (Hughes, Parisi et al. 2005).

In a subsequent prospective multicenter observational trial of high-grade glioma patients treated with standard chemoradiotherapy, 40% of patients had CD4 counts <200 cells/mm^3 by 2 months after initiating therapy (Grossman, Ye et al. 2011). Importantly, after adjusting for known prognostic factors, patients with CD4 counts <200 cells/mm^3 had significantly inferior median survival as compared to those with higher CD4 counts (13.1 vs. 19.7 mos, p=0.002). Interestingly, the cause of death was attributable to early tumor progression, and not to opportunistic infections as was the original hypothesis. Thus, these findings highlight the putative importance of radiosensitive circulating CD4 lymphocytes on tumor control and survival, implicating an immunologic mechanism.

Significantly, this finding is not restricted to gliomas. The prognostic value of lymphopenia for survival was analyzed in 3 databases of previously reported prospective multicenter studies: 1) FEC chemotherapy in metastatic breast carcinoma; 2) CYVADIC in advanced soft-tissue sarcoma (EORTC-STBSG 62791); and, 3) prospective, consecutive phase III studies of aggressive diffuse large-cell non-Hodgkin's lymphomas conducted at Bérard center between 1987 and 1993 (Ray-Coquard, Cropet et al. 2009). On univariate analysis, lymphopenia <1000/μL significantly correlated with overall survival in patients with metastatic breast cancer (median 10 vs. 14 months, p <0.0001), advanced soft-tissue sarcoma (median 5 vs. 10 months, p <0.01), and non-Hodgkin's lymphoma (median 11 vs. 94 months, p <0.0001). In a multivariate analysis Cox model, lymphopenia was an independent prognostic factor for overall survival in metastatic breast cancer (RR: 1.8; 95%CI 1.3–2.4); in advanced soft-tissue sarcoma (RR: 1.46; 95%CI 1.0–2.1); and in non-Hodgkin's lymphoma (RR: 1.48; 95%CI 1.03–2.1). These findings demonstrate that lymphopenia is an independent prognostic factor for overall and progression-free survival in several malignancies.

As a result of steep dose fall-off and narrow penumbrae, one advantage of proton beam therapy is its lower integral dose to the brain and hence the blood compartment circulating through the brain. Given the circulating nature of CD4 lymphocytes, we hypothesize that the use of proton beam therapy, as compared to photon IMRT or conventional photon radiotherapy, will be associated with less decline in CD4 counts during and following chemoradiotherapy due to reduced overall circulating blood volume irradiation, and that this may represent one potential

mechanism for improved treatment efficacy with proton beam therapy. This hypothesis will be assessed as an exploratory endpoint in this trial through the serial collection of CD4 lymphocytes and an analysis of overall survival as a function of CD4 lymphopenia.

1.6 Stratification (2/16/17)

Given the heterogeneous nature of GBM, stratification will be crucial in the design and conduct of this trial to ensure balance between arms, especially given the diversity of participating NRG institutions. Therefore, we propose a clinical and molecular stratification approach, using MGMT status and RPA class.

Clinical parameters associated with prognosis for patients with GBM have been identified and used as a basis for stratification in the past. For the majority of prior RTOG GBM trials, patient stratification has relied on clinical-pathologic risk factors as described by the RTOG recursive partitioning analysis (RPA) classification (Curran, Scott et al. 1993, Li, Wang et al. 2010). More recently, molecular markers associated with prognosis have been identified, with the most widely used marker being promoter methylation status of the gene encoding O^6-methylguanine DNA methyltransferase (*MGMT)*. In the RTOG 0525 trial comparing standard-dose temozolomide to dose-dense temozolomide, MGMT methylation status was used for patient stratification based on results from the EORTC 26981/22981, National Cancer Institute of Canada (NCIC) CE3 trial, which showed that this epigenetic variation predicted for improved survival (Hegi, Diserens et al. 2005). The current trial will utilize MGMT methylation status for molecular stratification. A number of methodologies have been developed to determine MGMT status, including quantitative PCR, pyrosequencing and direct PCR amplification. Given that there is no accepted national or international standard on how to perform the MGMT assay, this trial will utilize a central CLIA-certified laboratory (MD Anderson Cancer Center Molecular Diagnostics Lab; MDACC-MDL) for MGMT analysis.

1.6.1 Submission of Tissue for MGMT Analysis

The process of submitting tumor tissue for MGMT analysis has been fully developed and validated in prior RTOG studies. Specifically, mandatory tissue submission (1 square centimeter of tumor when cut onto slide) was required for randomization in both RTOG 0525 and RTOG 0825. For centers participating in this study, FFPE tumor tissue blocks will be sent to the NRG Oncology Biospecimen Bank at University of California, San Francisco for central pathology review (K. Aldape) and MGMT analysis (MDACC-MDL). If MGMT can be assessed locally by LabCorp or MDACC-MDL, then the official LabCorp or MDACC-MDL result must be submitted to the NRG Oncology Biospecimen Bank per Section 10.2 on or before postoperative day 40 at the time of tissue submission. The site's local MGMT report from LabCorp or MDACC-MDL will then be used to stratify the patient. A post-stratification MGMT central review (MDACC-MDL) will be performed if stratification was based on a LabCorp result. If MGMT cannot be assessed locally by LabCorp or MDACC-MDL, then tumor tissue must be sent by overnight courier (FedEx/UPS) and received on or before postoperative calendar day 30 for central MGMT analysis to be performed at MDACC-MDL and used for patient stratification. Results will be conveyed to NRG Oncology within 10 business days of receipt of tissue at the NRG Oncology Biospecimen bank. Sites not able to assess MGMT at LabCorp or MDACC-MDL locally and not able to submit tumor tissue to be received on or before postoperative calendar day 30, may NOT enroll patients on this trial, as central pathology review and MDACC-MDL will not be complete in time for the patient to start treatment within 49 calendar days following surgery (see Section 10 for details).

1.7 Neurocognitive Function and Patient-Reported Outcomes

Brain tumors affect brain functioning, and interventions such as chemotherapy and radiation therapy may also impact brain functions. Therefore, tumor recurrence, survival, and time to progression endpoints may not fully describe the outcome of an intervention unless added information regarding neurocognitive function, and disease and treatment-related symptoms are also considered as therapeutic outcomes.

As noted earlier, photon IMRT and proton beam radiotherapy represent novel radiotherapy approaches to intensifying local therapy. Given their conformal dose distribution and ability to spare adjacent normal tissue structures, including normal brain parenchyma, it is postulated that higher total doses can be delivered safely. Furthermore, proton beam therapy is associated with significantly lower integral dose to the normal brain as compared to photon IMRT. Evaluating the impact of these approaches on both the acute and long-term effects of radiation therapy and the potential benefit of improved tumor control with less exposure of surrounding brain is an important secondary endpoint of this study. Recently, the potential advantages of proton radiation therapy in terms of preservation of cognitive function have been reported. Merchant et al (2008) demonstrated in models of radiation dose-cognitive effects the theoretical advantage of treatment with protons compared to photons. Kahalley et al. (2013) reported that children treated with proton radiation evidenced generally stable cognitive function over 3 years of follow up compared to children treated with photon radiation therapy who demonstrated progressive cognitive decline over time.

1.7.1 Neurocognitive Function

A brief, sensitive, repeatable, highly standardized, objective battery of cognitive tests has been utilized in numerous brain tumor clinical trials (Groves 1999; Levin 2002). Objective assessment of neurocognitive function provides unique information about neurologic function that frequently is not captured by self-report measures (Cull 1996). This battery has been demonstrated to be practical in terms of burden on the patient, with good compliance in multicenter trials (Gilbert 2014; Meyers 2004; Wefel 2011). Neurocognitive function has been demonstrated to predict tumor progression (Meyers 2003) and to independently predict survival for patients with central nervous system tumors (Meyers 2004; Meyers 2000; Klein 2003; Johnson et al., 2012; Armstrong et al., 2013).

1.7.2 Patient-Reported Outcomes (PROs)

Symptom assessment measures such as the MDASI-BT have been specifically developed in patients with primary brain tumors to capture patient self-reports of symptom severity and interference with daily activities. This tool represents a modification of the widely used and validated MDASI, with particular attention to symptoms common in patients with brain tumors (Armstrong 2006). The MDASI has been used in a variety of cancer populations as an indicator of treatment response and predictor of survival (Cleeland, Mendoza et al. 2000, Rosenthal, Mendoza et al. 2008, Park, Janjan et al. 2009, Wang, Shi et al. 2010).

PRO questionnaires are used to capture the impact of a therapy from the patient's perspective, without interpretation by anyone else. This study will include the M.D. Anderson Symptom Inventory-Brain Tumor, designed to measure the severity and interference of symptoms. Symptom assessment measures such as the M.D. Anderson Symptom Inventory Brain Tumor (MDASI-BT) have been specifically developed in patients with primary brain tumors to capture patient self-reports of symptom severity and interference with daily activities and has demonstrated reliability and validity in the primary brain tumor patient population, including predictive validity for tumor recurrence (Armstrong 2011**a**).

By formally assessing patients' neurocognitive function and perceived cognitive and other disease and treatment associated symptoms we will be able to critically evaluate the clinical benefit of potential survival gains associated with either photon IMRT or proton beam therapy as well as compare the results with similar data collected in the RTOG 0525 and RTOG 0825 preceding trials. If both experimental arms demonstrate superior OS compared to the control arm then evaluation of cognitive function between arms will be critical to determining which treatment should be moved forward in a phase III trial.

1.8 Advanced MR Imaging (8/7/15)

Response assessment in GBM is difficult as a result of the frequent occurrence of early imaging changes indistinguishable from tumor progression. Pseudoprogression occurs in upwards of 50% of all GBM patients treated with combined chemoradiation and often leads to unwarranted treatment adjustments that may compromise treatment efficacy. In fact, there is evidence to suggest that further dose intensification leads to higher rates of pseudoprogression (Tsien,

Brown et al. 2012). Therefore, as a matter of good patient care, every effort should be made to obtain advanced imaging to distinguish pseudoprogression from true tumor progression. Currently, there are no established, reliable methods of distinguishing pseudoprogression.

Dynamic acquisition of T2*-weighted MR imaging during intravenous injection of Gd-DTPA allows estimations of cerebral (tumor) blood volume, bolus transit time and flow. (Cao, JCO 2006) Perfusion imaging provides evidence of tumor viability and is sensitive to tumor vascular properties and transport kinetics following therapy. (Galban, 2009) Dynamic susceptibility contrast (DSC) T2*-weighted imaging is the method of choice to map whole-brain perfusion properties (Cao, JMRI 2006). Quantitative imaging analysis methods are highly sensitive to analyzing treatment-induced cellularity and hemodynamic alterations within the tumor (Hamstra, 2008; Moffat 2005).

In a preliminary study, MR perfusion improved response assessments in patients receiving chemo-radiotherapy (Tsien, Galban et al. 2010) by consistently and reliably distinguishing patients with true progression from patients with pseudoprogression. These single-institution data are the most promising advanced MRI imaging biomarkers for prediction of pseudoprogression, response, and overall survival. For the present exploratory endpoint, we wish to establish the ability of advanced MR imaging to consistently and reliably discriminate between true and pseudoprogression in a multi-institutional setting.

Initial results from the University of Michigan as well as others also demonstrated that baseline high tumor perfusion (or high relative cerebral blood volume rCBV) has been shown to correlate with shorter survival irrespective of grade (Law, 2008) and response to radiation therapy. (Cao, Tsien et al. 2006) A novel quantitative voxel-by voxel method of image analysis, parametric response maps PRM_{ADC} and PRM_{rCBV} are important early, predictors of treatment response and overall survival in high grade gliomas. (Galban, 2009) An additional exploratory aim is to confirm these findings in a larger, multi-institutional trial.

Advanced imaging will provide important supplementary information to physicians in the response assessment for patients randomized to the experimental arm. (See Section 11.4) Advanced MRI scans will be obtained at baseline and at subsequent follow-up time-points at designated, pre-approved sites on subjects consented and enrolled into the advanced imaging component. See Appendix VIII regarding site qualification.

1.9 Summary

In summary, contemporary studies of standard postoperative chemoradiotherapy for patients with GBM have demonstrated a high rate of local failure and poor median survival of 15-16 months. Tumor hypoxia and its promotion of malignant behavior, angiogenesis, and stem cell survival present an important hurdle to treatment efficacy. Approaches to local therapy intensification, including radiotherapy dose and dose-per-fraction escalation, may overcome hypoxia-related treatment resistance. Multiple phase I and phase II studies have demonstrated the feasibility and tolerability of dose escalation with concurrent nitrosourea chemotherapy and suggest a possible survival improvement. Since the introduction of temozolomide as a potent radiosensitizer, the question of radiotherapy intensification has not been tested in a large randomized trial.

Thus, we propose a randomized phase II study of dose-escalated and -intensified photon IMRT or proton beam therapy versus standard-dose photon irradiation, along the backbone of concomitant and adjuvant temozolomide, for patients with newly diagnosed GBM. The primary endpoint of this study is improvement in overall survival, with multiple secondary and exploratory endpoints. Additional correlative analyses will study the differential impact of CD4 lymphopenia on treatment outcomes; compare treatment arms in terms of symptom burden; and explore advanced magnetic resonance imaging biomarkers to discriminate between pseudo-progression and true progression.

2.0 OBJECTIVES

2.1 Primary

To determine if dose-escalated and -intensified photon IMRT or proton beam therapy (using a dose-per-fraction escalation with simultaneous integrated boost) with concomitant and adjuvant temozolomide improves overall survival, as compared to standard-dose photon irradiation with concomitant and adjuvant temozolomide.

2.2 Secondary

2.2.1 To indirectly compare dose-escalated and -intensified photon IMRT to dose-escalated and -intensified proton beam therapy in terms of overall survival.

2.2.2 To indirectly compare and record toxicities of dose-escalated and -intensified photon IMRT versus dose-escalated and -intensified proton beam therapy and directly compare the toxicities of these approaches versus standard-dose photon irradiation on the backbone of concomitant and adjuvant temozolomide

2.2.3 To determine if dose-escalated and -intensified photon IMRT or proton beam therapy (using a dose-per-fraction escalation with simultaneous integrated boost) with concomitant and adjuvant temozolomide improves perceived cognitive symptom severity, as compared to standard-dose photon irradiation with concomitant and adjuvant temozolomide.

2.2.4 To determine if dose-escalated and -intensified photon IMRT or proton beam therapy (using a dose-per-fraction escalation with simultaneous integrated boost) with concomitant and adjuvant temozolomide improves neurocognitive function, as compared to standard-dose photon irradiation with concomitant and adjuvant temozolomide.

2.2.5 To indirectly determine if dose-escalated and -intensified proton beam therapy with concomitant and adjuvant temozolomide improves perceived cognitive symptom severity, as compared to dose-escalated and -intensified photon IMRT, and to directly compare symptom burden with these approaches versus standard-dose photon irradiation on the backbone of concomitant and adjuvant temozolomide

2.2.6 To indirectly determine if dose-escalated and -intensified proton beam therapy with concomitant and adjuvant temozolomide improves neurocognitive function, as compared to dose-escalated and -intensified photon IMRT, and to directly compare neurocognitive function with these approaches versus standard-dose photon irradiation on the backbone of concomitant and adjuvant temozolomide

2.3 Exploratory

2.3.1 Tissue banking for future translational science projects that will be determined based on the state of the science at the time the primary endpoint is reported and will be submitted to NCI for review and approval.

2.3.2 To prospectively compare CD4 lymphopenia between dose-escalated and intensified proton beam therapy, dose-escalated and -intensified photon IMRT, and standard-dose photon irradiation and determine whether CD4 lymphopenia impacts overall survival.

2.3.3 To explore the most appropriate and clinically relevant technological parameters to ensure quality and effectiveness throughout radiation therapy processes, including imaging, simulation, patient immobilization, target and critical structure definition, treatment planning, image guidance and delivery.

- To establish feasibility and clinical relevancy of quality assurance guidelines
- To evaluate efficacy of quality assurance tools

2.3.4 To explore the most appropriate and clinically relevant advanced and standard MRI imaging parameters

- To evaluate the feasibility of differentiating pseudo-progression and true progression in a multi institutional setting using MR diffusion and perfusion imaging.
- To evaluate for early, imaging biomarkers of response and overall survival.

3.0 PATIENT SELECTION
NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (2/16/17)
For questions concerning eligibility, please contact NRG Data Management.

Prior to STEP 1 REGISTRATION

3.1.1 A diagnostic contrast-enhanced MRI (no other scan type allowed) of the brain must be performed postoperatively. The residual enhancing tumor and/or resection cavity must have a maximal diameter of 5 cm or less (as specified in the aforementioned University of Michigan phase I/II trial of dose-intensification with temozolomide). The tumor diameter will be the greatest diameter as measured on the contrast-enhanced postoperative MRI and will include residual disease and/or the postoperative surgical cavity as appropriate.

- The postoperative brain MRI should be obtained within 72 hours of resection. If it is not obtained within 72 hours post-resection, then an MRI obtained 2 weeks or longer after surgery is required and can be utilized to ensure maximal diameter of residual tumor and/or resection cavity is 5cm or less.
- For cases where a gross total resection of enhancing tumor is performed, but postoperative surgical cavity is NOT identifiable, the patient will be excluded from the trial.

3.1.2 Tumor tissue must be available for submission for central pathology review.

Timing Requirements:

- **If MGMT has been assessed locally by LabCorps or MDACC-MDL:**
  - Tissue for central pathology review and central MGMT assessment and the official LabCorps or MDACC-MDL MGMT result must be received by the NRG Oncology Biospecimen Bank on or before postoperative calendar day 40.
  - The site's local MGMT report from LabCorp or MDACC-MDL will then be used to stratify the patient. A post-stratification MGMT central review will be performed, but Step 2 registration and protocol treatment can proceed without central review of MGMT.
  - Patients whose tissue for central pathology review and official LabCorps or MDACC-MDL MGMT result cannot be received by NRG Oncology Biospecimen Bank on or before 40 calendar days after surgery may NOT enroll on this trial, as central pathology review and stratification will not be complete in time for the patient to start treatment within 49 calendar days following surgery.

- **If MGMT has not been assessed locally by LabCorps or MDACC-MDL:**
  - Tissue for central pathology review and central MGMT assessment must be received by the NRG Oncology Biospecimen Bank on or before postoperative calendar day 30.
  - Central MGMT analysis will be performed at MDACC-MDL and used for patient stratification. Results will be conveyed to NRG Oncology within 10 business days of receipt of the tissue.

  Patients who have not had local MGMT assessment by LabCorps or MDACC-MDL and whose tissue for central pathology review cannot be received by NRG Oncology Biospecimen Bank on or before 30 calendar days after surgery may NOT enroll on this trial, as central pathology review and stratification will not be complete in time for the patient to start treatment within 49 calendar days following surgery.

Tissue Requirements:

- Patients must have at least 1 block of tumor tissue; submission of 2 blocks is strongly encouraged to maximize the chances of eligibility. In total, at least 1 cubic centimeter of tissue composed primarily of tumor must be present.

- Submission of accompanying H&E slide(s) is MANDATORY.
- Diagnosis must be made by surgical excision, either partial or complete. Stereotactic biopsy and cavitronic ultrasonic surgical (CUSA) techniques are not allowed.

3.1.3 The tumor must be located in the supratentorial compartment only (any component involving the brain stem or cerebellum is not allowed).

3.1.4 Patients must provide study-specific informed consent prior to step 1 registration.

3.1.5 Prior to STEP 2 REGISTRATION
Histologically proven diagnosis of glioblastoma (WHO grade IV) **confirmed by central review** prior to step 2 registration (See Section 10 for details)

3.1.6 Tumor tissue that is **determined by central pathology review** prior to step 2 registration to be of sufficient quantity for central analysis of MGMT status (See Section 10).

3.1.7 History/physical examination within 28 days prior to step 2 registration.

3.1.8 The patient must have recovered from effects of surgery, postoperative infection, and other complications within 28 days prior to step 2 registration.

3.1.9 Documentation of steroid doses within 28 days prior to step 2 registration.

3.1.10 Karnofsky performance status ≥ 70 within 28 days prior to step 2 registration.

3.1.11 Age ≥ 18.

3.1.12 CBC/differential obtained within 28 days prior to step 2 registration, with adequate bone marrow function defined as follows:
- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 10.0 g/dl (Note: the use of transfusion or other intervention to achieve Hgb ≥10.0 g/dl is acceptable);

3.1.13 Adequate hepatic function within 28 days prior to step 2 registration, as defined below:
- Bilirubin ≤ 1.5 ULN
- ALT and AST ≤ 3 x ULN

3.1.14 Negative serum pregnancy test obtained for females of child-bearing potential within 28 days prior to step 2 registration

3.1.15 As of Amendment 2, if the registering site is a photon center (registering patients to Group I), the patient must agree to participate in the advanced imaging sub-study.

3.2 Conditions for Patient Ineligibility (8/7/15)

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease-free for a minimum of 3 years. (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible)

3.2.2 Recurrent or multifocal malignant gliomas.

3.2.3 Any site of distant disease (for example, drop metastases from the GBM tumor site).

3.2.4 Prior chemotherapy or radiosensitizers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable (except temozolomide).

3.2.5 Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment are not permitted. See Section 3.2.1.

3.2.6 Prior radiotherapy to the head or neck (except for T1 glottic cancer), resulting in overlap of radiation fields

3.2.7 Severe, active co-morbidity, defined as follows:
- Unstable angina at step 2 registration
- Transmural myocardial infarction within the last 6 months prior to step 2 registration
  Evidence of recent myocardial infarction or ischemia by the findings of S-T elevations of ≥ 2 mm using the analysis of an EKG performed within 28 days prior to step 2 registration. (Note: EKG to be performed only if clinical suspicion of cardiac issue.)
- New York Heart Association grade II or greater congestive heart failure requiring hospitalization within 12 months prior to step 2 registration.
- Serious and inadequately controlled arrhythmia at step 2 registration

- ☐ Serious or non-healing wound, ulcer or bone fracture or history of abdominal fistula, intra-abdominal abscess requiring major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to step 2 registration, with the exception of the craniotomy for surgical resection
- ☐ Acute bacterial or fungal infection requiring intravenous antibiotics at the time of step 2 registration
- ☐ Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.
- ☐ Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of step 2 registration
- ☐ Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is because the treatments involved in this protocol may be significantly immunosuppressive with potentially fatal outcomes in patients already immunosuppressed.
- ☐ Any other severe immunocompromised condition.
- ☐ Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the treating physician may put the patient at high risk for radiation toxicity.
- ☐ End-stage renal disease (ie, on dialysis or dialysis has been recommended).
- ☐ Any other major medical illnesses or psychiatric treatments that in the investigator's opinion will prevent administration or completion of protocol therapy.

3.2.8 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.9 Patents treated on any other therapeutic clinical protocols within 30 days prior to step 2 registration.

3.2.10 Inability to undergo MRI (e.g., due to safety reasons, such as presence of a pacemaker, or severe claustrophobia).

3.2.11 Postoperative tumor plus surgical bed size exceeds 5 cm in maximum diameter.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility. See Section 3 for eligibility-related assessments.

4.1 Highly Recommended Evaluations/Management

Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required.

- ☐ CD4 lymphocyte count prior to initiation of chemoradiotherapy.

5.0 REGISTRATION PROCEDURES (2/16/17)

Access requirements for OPEN, Medidata Rave, and TRIAD:

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at

5.1 Radiation-Specific Pre-Registration Requirements (8/7/15)

All proton centers must be able to deliver photon therapy or partner with a photon therapy site for patients randomized to Arm A2. It is recommended that proton sites not able to deliver photon therapy discuss logistics for a treatment partnership with partnering sites prior to registering patients, See the beginning of Section 12 for data submission logistics pertinent to this partnership.

NOTE: IF YOUR SITE IS CREDENTIALED FOR PROTONS FOR THIS TRIAL YOU MUST REGISTER TO GROUP II ONLY.

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study.

IMRT credentialing is mandatory for all sites.

Proton therapy may be used on this protocol if the proton therapy treatment modality to be used has been approved by the IROC Houston QA Center and other credentialing procedures described below have been met. Investigators using proton therapy must comply with the NCI proton guidelines for the Use of Proton Radiation Therapy in NCI Sponsored Cooperative Group Clinical Trials, which are available on the website of IROC Houston.

RT Credentialing Requirements	**Web Link for Procedures and Instructions: IROC Houston Website:** http://irochouston.mdanderson.org			
	Treatment Modality			**Key Information**
	3DCRT	**Photons IMRT**	**Proton**	
Facility Questionnaire	X	X	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link .
Credentialing Status inquiry form		X	X	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org) .
Knowledge Assessment			X	The Knowledge Assessment Form must be successfully completed prior to the enrollment of the first patient and is

				available on the IROC Houston website at http://irochouston.mdanderson.org
Phantom Irradiation		X	X	An anthropomorphic phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org).
Credentialing Notification Issued to:				
Institution				IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

If an institution is already credentialed for IMRT, 3D-CRT does not require separate credentialing.

5.2 Pre-Registration Requirements for Sites Participating in the Advanced Imaging Sub-Study (8/7/15)

For information on site qualification for sites participating in the advanced imaging sub-study, contact the ACR Clinical Research Center at imagearchive@acr.org and see Appendix VIII.

5.3 Digital RT Data Submission to NRG Using TRIAD

TRIAD is the American College of Radiology's (ACR) image exchange application and it is used by NRG. TRIAD provides sites participating in NRG clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the RTOG website Core Lab tab.

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

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

5.4 Regulatory Pre-Registration Requirements (2/16/17)

5.4.1 Neurocognitive Credentialing

Institutions must meet certification requirements for administering neurocognitive assessments. The healthcare professional (e.g., nurse, psychologist) who is responsible for test administration in this study must be pre-certified by Dr. Wefel (See Appendix VII).

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

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

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:

Site registration forms may be downloaded from the NRG-BN001 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the NRG Oncology link to expand, then select trial protocol # NRG-BN001
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for NRG-BN001 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)
- CTSU RT Facilities Inventory Form
  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility
- Neurocognitive Credentialing certification (See Appendix VII)
- IRB/REB approved consent (Canadian sites only: English and native language versions*)
  ***Note**: Canadian Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology (described below).

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

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

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

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

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

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

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

5.4.3 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

NOTE: Canadian institutions may enroll patients only to Group 1/Photon Treatment

Prior to clinical trial commencement, Canadian institutions must also complete and fax (215-569-0206) or e-mail (**CTSURegulatory@ctsu.coccg.org**) to the CTSU Regulatory Office:

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

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

5.5 Registration (8/7/15)

OPEN Registration Instructions

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

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster. See Section 5.0 for obtaining a CTEP-IAM account. All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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

6.0 RADIATION THERAPY (8/7/15)

See Section 5.3 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

Treatment must begin ≤ 49 calendar days after surgery. No earlier timeline is set as long as the incision has healed adequately; this usually takes at least 2 weeks.

The reader should refer to the schema at the beginning of the protocol before reading this section.

Postoperative MRI with T2/FLAIR and contrast-enhanced T1 sequences is required and should be obtained within 72 hours of resection. If it is not obtained within 72 hours post-resection, then an MRI obtained 2 weeks or longer after surgery is required . **I**n addition, if >3 weeks have elapsed between surgical resection and radiotherapy planning, a repeat postoperative MRI with T2/FLAIR and contrast-enhanced T1 sequences is highly recommended for radiotherapy planning purposes. The postoperative MRI scan used for planning MUST be submitted as a complete series along with the treatment.

Proton dose will be reported in Gy (relative biologic effectiveness, RBE), where 1 Gy (RBE) = proton dose Gy x RBE, RBE = 1.1.

NOTE: The 1st 2 patients enrolled by a proton center onto ARM C (PROTON) will require a Pre-Treatment Review. The patient cannot start treatment until they have received approval from IROC-Phila. The Pre-Treatment review process requires 3 business days from the receipt of complete data. See Section 12.2 for specifics on submission requirements.

6.1 Treatment Technology

3DCRT and IMRT are allowed in Arms A1 and A2. IMRT with a simultaneous integrated boost is required for Arm B. Fixed-gantry IMRT, helical tomotherapy, or VMAT can be used for Arms A1, A2, or B. Proton therapy with simultaneous integrated boost is required for Arm C. The proton treatment modalities are listed in Section 6.1.2.

For Arm B, if the IMRT system is not operational, then no more than 5 fractions of 3DCRT can be delivered. For Arm C, if the proton therapy system is not operational, then no more than 5 fractions of 3DCRT and/or IMRT can be delivered.

6.1.1 Photon Reference Arm or Photon IMRT Experimental Arm

All photon treatments shall be delivered with megavoltage machines of a minimum energy of 6 MV photons. Selection of the appropriate photon energy(ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. Source-to-skin distance for SSD techniques or source-to-axis distance for SAD techniques must be at least 80 cm. The photon **reference** arm will be treated with a **sequential** boost to the contrast-enhancing region of the target. The photon **experimental** arm will use a **simultaneous** integrated boost technique. Electron, particle, or implant boost is not permissible for the photon arms. Patient-specific quality assurance is highly recommended prior to start of treatment and is described in Section 6.8.

6.1.2 Proton Experimental Arm

Proton beam therapy will be delivered with either passive scattered, uniform scanning beam, pencil beam scanning (PBS) or intensity modulated proton therapy (IMPT) techniques depending on the facility's experience and equipment. Patching techniques will be allowed. Selected proton energies should be high enough to adequately provide target coverage. Range shifters may be used to make fine adjustment of the proton range. Both passive scattering and uniform scanning beams will employ customized apertures and compensators to shape the fields laterally and distally. PBS techniques where each field is optimized to deliver a uniform dose to the target volume are permitted. Multi-field optimization or intensity modulated proton therapy will be allowed on this protocol with the restriction that the distal edge of a field is not patched to another field. Patient-specific quality assurance is highly recommended prior to start of treatment and is described in Section 6.8.

6.2 Immobilization, Simulation, and Imaging for Structure Definition (8/7/15)

6.2.1 Photon Reference Arm or Photon IMRT Experimental Arm

Patients will be treated in a supine position and immobilized with a thermoplastic mask and headrest. Additional immobilization devices such as a bite block are permitted.

A planning CT scan will be obtained of the cranial contents and will be fused with the pre- and post-operative MRI scans; if the pre-operative MRI scan is not available for electronic fusion purposes, fusion with only the post-operative MRI scan is permitted. However, it is strongly recommended that the pre-operative MRI scan be accessed for evaluation to assist in the planning process. The post-operative MRI scan must be obtained within 72 hours or 2 weeks or longer after surgical resection. If >3 weeks have elapsed between surgical resection and radiotherapy planning, a repeat postoperative MRI with T2/FLAIR and contrast-enhanced T1 sequences is highly recommended for radiotherapy planning purposes. Target volume

delineation will be based upon the postoperative contrast-enhanced MRI. Preoperative imaging should be used for correlation and improved identification.

6.2.2 Proton Experimental Arm

Patients will be treated in a supine or seated position and immobilized with a proton-compatible thermoplastic mask and headrest. Additional immobilization devices such as a bite block may be used.

Proton treatment plans will be based upon scans obtained with a CT scanner for which the institution has defined an imaging protocol for protons which establishes the relationship between CT number and the stopping power ratios. A CT scan will be obtained of the cranial contents and will be fused with the pre- and post-operative MRI scans. The post-operative MRI scan must be obtained within 72 hours or 2 weeks or longer after surgical resection. If >3 weeks have elapsed between surgical resection and radiotherapy planning, a repeat postoperative MRI with T2/FLAIR and contrast-enhanced T1 sequences is highly recommended for radiotherapy planning purposes. Target volume delineation will be based upon postoperative contrast-enhanced MRI. Preoperative imaging should be used for correlation and improved identification.

6.3 Definition of Target Volumes and Margins and Standardized Structure Naming (2/16/17)

Note: All structures in the table below must be contoured and labeled for digital RT data submission as listed in the table below. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

Photon Control Arm

Standard Name	Description
CTV_4600	CTV to receive 46 Gy in 23 fractions
PTV_4600	PTV to receive 46 Gy in 23 fractions
CTV_6000	CTV to receive 60 Gy in 30 fractions
PTV_6000	PTV to receive 60 Gy in 30 fractions

Photon IMRT Experimental Arm

Standard Name	Description
CTV_5000	CTV to receive 50 Gy in 30 fractions
PTV_5000	PTV to receive 50 Gy in 30 fractions
CTV_7500	CTV to receive 75 Gy in 30 fractions
PTV_7500	PTV to receive 75 Gy in 30 fractions

Proton Therapy Experimental Arm

Standard Name	Description
CTV_5000	CTV to receive 50 Gy(RBE) in 30 fractions
PTV_5000	PTV to receive 50 Gy(RBE) in 30 fractions
CTV_7500	CTV to receive 75 Gy(RBE) in 30 fractions
PTV_7500	PTV to receive 75 Gy(RBE) in 30 fractions

6.3.2 Margin Definitions

CTV_4600 and CTV_5000 - Either the T2 or FLAIR abnormalities on the post-operative MRI scan, inclusive of all contrast-enhancing T1 abnormality on the postoperative MRI and the surgical cavity, plus a margin of 2 cm, which may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc. If no surrounding edema is present, CTV should include postoperative MRI enhancement and the surgical resection cavity plus a 2-cm margin, with reductions permitted as described above.

CTV_6000 - Contrast-enhancing T1 abnormality and the surgical cavity on the post-operative

MRI scan plus a margin of 2 cm. The CTV_6000 margin may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc.

CTV_7500 - Contrast-enhancing T1 abnormality and the surgical cavity on the post-operative MRI scan plus a margin of 5 mm. The CTV_7500 margin may be reduced around natural barriers to tumor growth such as the skull, ventricles, falx, etc.

PTV_4600, PTV_5000, PTV_6000, **and PTV_7500** - In general the PTV is the CTV plus a geometric 4 mm expansion in all dimensions. PTV may extend beyond bony margins and the skin surface.

Special considerations are needed for proton treatments. In this situation the PTV is determined from CTV based on beam arrangement and will take into account lateral setup uncertainty as well as proton range uncertainty. For each beam, a 4 mm lateral margin will be added while the proton beam distal and proximal target margins will be based on the proton range uncertainty (see Section 6.7.3). The PTV may not extend beyond bony margins or the skin surface. The PTV is defined as the union of the beam specific PTVs and will be used to report dose, per ICRU 78.

6.4 Definition of Critical Structures and Margins (2/16/17)

Note: All structures listed in the table below must be contoured and labeled for digital RT data submission as listed. (As noted in the table, contouring of the lacrimal glands is optional). Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

- All structures should be contoured on the planning CT, using the postoperative MRI for guidance. Due to variance in eye position between the CT and MRI, if possible, the lenses, retinae, and optic nerves should be contoured using the CT dataset only.
- Special consideration should be given to avoid doses greater than the prescription dose within the scalp as well as limiting exit dose through the oral cavity and mucosa.

Standard Name	Description	Detailed Specification
Lens_L	Left lens	Due to variance in eye position between the CT and MRI, if possible, the left lens should be contoured using the CT dataset only.
Lens_R	Right lens	Due to variance in eye position between the CT and MRI, if possible, the right lens should be contoured using the CT dataset only.
Retina_L	Left retina	Due to variance in eye position between the CT and MRI, if possible, the left retina should be contoured using the CT dataset only.
Retina_R	Right retina	Due to variance in eye position between the CT and MRI, if possible, the right retina should be contoured using the CT dataset only.
OpticNerve_L	Left optic nerve	Due to variance in eye position between the CT and MRI, if possible, the left optic nerve should be contoured using the CT dataset only.
OpticNerve_R	Right optic nerve	Due to variance in eye position between the CT and MRI, if possible, the right optic nerve should be contoured using the CT dataset only.
OptNrv_L_PRV	Left optic nerve planning risk volume	Left optic nerve should be expanded by a volumetric expansion of 3mm.
OptNrv_R_PRV	Right optic nerve planning risk volume	Right optic nerve should be expanded by a volumetric expansion of 3mm.

OpticChiasm	Right optic nerve	Located above the pituitary fossa, the optic chiasm includes both anterior and posterior limbs. It is best visualized on postoperative T2/FLAIR MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.
OpticChiasm_PRV	Optic chiasm planning risk volume	Optic chiasm should be expanded by a volumetric expansion of 3mm.
BrainStem	Brainstem	Brainstem contour should include all three components: midbrain, pons, and medulla. The brainstem is bordered superiorly by the tentorial incisure and inferiorly by the foramen magnum. It can be visualized on postoperative MRI sequence, but should be confirmed on CT dataset due to potential variation in CT/MRI fusion.
BrainStemSurf	Brainstem surface	Brainstem surface includes only the ventral 3mm of the brainstem from the 9 o'clock to the 3 o'clock position in each axial slice.
BrainStemCore	Brainstem core	Brainstem core includes the brainstem outside the brainstem surface in each axial slice of the brainstem.
SpinalCord	Spinal cord	Spinal cord should be contoured, wherever possible, on the CT dataset only.
Brain	Whole brain parenchyma	Whole brain parenchyma includes all intracranial contents, inclusive of target volumes. Because some volumetric change could have occurred in the whole brain parenchyma due to evolving post-operative changes, it is recommended, wherever possible to contour the whole brain parenchyma using the CT dataset only
Lacrimal_L	Left lacrimal gland **Contouring Optional**	Although not mandated, it is recommended that the dose to the left lacrimal gland be monitored and wherever possible, published dose constraints be respected.
Lacrimal_R	Right lacrimal gland **Contouring Optional**	Although not mandated, it is recommended that the dose to the left lacrimal gland be monitored and wherever possible, published dose constraints be respected.

6.5 Dose Prescription

Photon Reference Arm A1 or A2

Target Standard Name	**Dose (Gy)**	**Fraction Size (Gy)**	**# of fractions**	**Dose specification technique**
PTV_4600	46	2.0	23	Exactly 95% of PTV receives 46 Gy
PTV_6000	60	2.0	30	≥95% of PTV should receive ≥60 Gy

Photon IMRT Experimental Arm B

Target Standard Name	**Dose (Gy)**	**Fraction Size (Gy)**	**# of fractions**	**Dose specification technique**
PTV_5000	50	1.67	30	Exactly 95% of PTV receives ≥50 Gy
PTV_7500	75	2.5	30	≥95% of PTV should receive ≥75 Gy

Proton Therapy Experimental Arm C

Target Standard Name	**Dose [Gy(RBE)]**	**Fraction Size [Gy(RBE)]**	**# of fractions**	**Dose specification technique**
PTV_5000	50	1.67	30	Exactly 95% of PTV receives ≥50 Gy
PTV_7500	75	2.5	30	≥95% of PTV should receive ≥75 Gy

6.6 Compliance Criteria (8/7/15)

Normalization of Dose: 95% of the PTV ($D_{95\%}$) should be covered by 100% of the prescription dose.

Target Volume Constraints and Compliance Criteria

Photon Reference Arm A1 or A2

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTV_4600	$D_{95\%}$(Gy)	Exactly 46	≥43.7
PTV_6000	$D_{95\%}$ (Gy)	59.25-60.75	57.0-59.25 or 60.75-63.0
	$D_{10\%}$(Gy)	≤63	63-65.12
	$D_{0.03cc}$(Gy)	≤64.0	64.0-66.0

Photon IMRT Experimental Arm B

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTV_5000	$D_{95\%}$(Gy)	Exactly 50	≥47.5
PTV_7500	$D_{95\%}$ (Gy)	74.25-75.75	71.25-74.25 or 75.75-78.75
	$D_{10\%}$(Gy)	≤78.7	78.7-81.4
	$D_{0.03cc}$(Gy)	≤80.0	80.0-82.5

Proton Experimental Arm C

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable
PTV_5000	$D_{95\%}$ [Gy(RBE)]	Exactly 50	≥47.5
PTV_7500	$D_{95\%}$ [Gy(RBE)]	74.25-75.75	71.25-74.25 or 75.75-78.75
	$D_{10\%}$[Gy(RBE)]	≤78.7	78.7-81.4
	$D_{0.03cc}$[Gy(RBE)]	≤80.0	80.0-82.5

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met as indicated in the table above.

Normal Structure Constraints and Compliance Criteria for Photon and Proton Therapy

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
SpinalCord[1]	D_{max}[Gy(RBE)]	≤50	
BrainStemCore	D_{max}[Gy(RBE)]	≤55	55-60
BrainStemSurf	D_{max}[Gy(RBE)]	≤55	55-64
OpticChiasm_PRV	D_{max}[Gy(RBE)]	≤55	55-60
OptNrv_L_PRV or OptNrv_R_ PRV[2]	D_{max}[Gy(RBE)]	≤55	55-60
Retina_L or Retina_R[3]	D_{max}[Gy(RBE)]	≤45	45-50
Brain	$D_{5\%}$[Gy(RBE)]	≤78.7	78.7-81.4
Lens_L or Lens_R[4]	D_{max}[Gy(RBE)]	≤7	7-10

D_{max} defined for a volume less than or equal to 0.03cc.

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met as indicated in the table above.
Exceptions:

1. **SpinalCord does not have a Variation Acceptable; Deviation Unacceptable occurs when SpinalCord dose limit for Per Protocol is not met.**
2. **Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met for both OptNrv_L_PRV and OptNrv_R_PRV; or OptcNrv_L_PRV if the patient does not have serviceable vision in the right eye; or OptNrv_R_PRV if the patient does not have serviceable vision in the left eye.**
3. **Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met for both Retina_L and Retina_R; or Retina_L if the patient does not have serviceable vision in the right eye; or Retina_R if the patient does not have serviceable vision in the left eye.**
4. **Exceeding the dose limits for Variation Acceptable for Lens_L or Lens_R will not be scored as Deviation Unacceptable.**

Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	Notes
Start date	≤ 7 weeks after surgery	Up to 8 weeks after surgery (56 days)	
Interruptions*	≤ 4 days	5-7 days	

*Patients randomized to the proton therapy experimental arm may receive up to 5 fractions with photons in the event the proton machine is not available.

6.7 Treatment Planning Procedures and Priorities

6.7.1 Photon Reference Arm A1 or A2 (3DCRT or IMRT)

Treatment Planning Procedures

Three-dimensional conformal radiotherapy or intensity-modulated radiotherapy will be used for patients enrolled in the photon reference arm. Using IMRT with the boost region treated with a simultaneous integrated boost technique is not allowed for reference treatment components of this protocol. Two treatment plans must be submitted for the reference treatment component of each arm: First, the large-field plan must be submitted showing coverage of the 46 Gy PTV. Second, a composite plan showing coverage of the 60 Gy PTV must be submitted.

Treatment Planning Priorities

1. SpinalCord
2. BrainStemCore
3. BrainStemSurf
4. OptChiasm_PRV
5. OptNrv_L_PRV and OptNrv_R_PRV
6. PTV_4600
7. PTV_6000
8. Brain
9. Retina_L and Retina_R
10. Lens_L and Lens_R

In the event that an OAR with higher priority than PTV_6000 is in immediate proximity to PTV_6000 such that dose to the OAR cannot be constrained within Unacceptable Deviation limits, then D95% for PTV_6000 should be lowered to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits. If this approach does not constrain the OAR with higher priority than PTV_6000 within Unacceptable Deviation limits, then D95% for PTV_6000 can be further lowered to below but as close as possible to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits; this will be scored as an Unacceptable Deviation for PTV_6000.

Dose Distribution Calculations

Dose matrix grid size must be 3mm x 3mm x 3mm or smaller.

Plan Review and Evaluation

Traditional DVHs and dose distribution displays will be used for plan review and evaluation. DVHs will also be used for retrospective outcome analyses.

6.7.2 Photon Experimental Arm B (IMRT)

Treatment Planning Procedures

Intensity modulated radiotherapy will be used for patients enrolled in the photon IMRT experimental arm. Three-dimensional conformal radiotherapy will not be permitted.

Treatment Planning Priorities

1. SpinalCord
2. BrainStemCore
3. BrainStemSurf
4. OptChiasm_PRV
5. OptNrv_L_PRV and OptNrv_R_PRV
6. PTV_5000
7. PTV_7500
8. Brain

9. Retina_L and Retina_R
10. Lens_L and Lens_R

Reducing PTV_7500 margins to meet treatment-planning priorities is not generally permissible. In the event that an OAR with higher priority than PTV_7500 is in immediate proximity to PTV_7500 such that dose to the OAR cannot be constrained within unacceptable deviation limits, a second PTV ($PTV_{overlap}$), defined as the overlap between the PTV_7500 and the particular OAR of concern, may be created (the overlap is the intersection between PTV and the OAR). Dose to the $PTV_{overlap}$ must be as close as permissible to 75 Gy while not exceeding the OAR unacceptable deviation limit.

Dose Distribution Calculations
Dose matrix grid size must be 3mm x 3mm x 3mm or smaller.

Plan Review and Evaluation
Traditional DVHs and dose distribution displays will be used for plan review and evaluation. DVHs will also be used for retrospective outcome analyses.

6.7.3 Proton Therapy Experimental Arm C

Treatment Planning Procedures

- Passively scattered proton therapy, uniform scanned proton beams, pencil beam scanning (PBS) proton therapy or intensity modulated proton therapy (IMPT) will be used for patients enrolled in the proton arm.
- PBS plans will be optimized so that each field homogeneously covers the dose to each target. Multi-field optimized IMPT plans will be allowed on this protocol with the restriction that the distal edge of a field is not patched to only one other field that is more than 90^{o} apart. However, if robust IMPT optimization is used (Liu W. 2012), there is no beam angle restriction.
- For proton planning, each beam has an individual and unique expansion from the CTV. In the plane perpendicular to the proton beam axis, the PTV expansion from the CTV is 4mm while the distal and proximal range margins will be calculated using established methods (Paganetti 2012) and determined by the individual institution's practice based on their local machine characteristics for the modality. In place of the beam specific PTV (bsPTV), a uniform 4 mm PTV expansion from CTV may be used as it will be a close approximation of the bsPTV for a target located within the brain.
- A block margin must be assigned depending on the penumbra specific to the proton beam being used. Note that proton beam penumbra is a function of proton energy and the distance between aperture + compensator and patient's anatomy. It may vary significantly from one clinical situation to another.
- To cover PTV_5000, at least two proton beams should be utilized. To cover PTV_7500, at least one additional proton beam may be necessary.
- Multiple minimally overlapping beams are encouraged to minimize skin dose. Care should also be taken to avoid beam angles that cause flash beyond the patient's body contour.
- Distal range uncertainty should be evaluated for each beam. Due to concerns of increasing LET at the distal edge, brainstem, spinal cord, and optic nerves/chiasm should not be exposed to distal range uncertainty from more than one beam. Within PTV_7500, whole-brain parenchyma should not be exposed to distal range uncertainty from more than one beam. Single proton beam plans will not be allowed.

Treatment Planning Priorities

1. SpinalCord
2. BrainStemCore
3. BrainStemSurf
4. OptChiasm_PRV
5. OptNrv_L_PRV and OptNrv_R_PRV

6. PTV_5000
7. PTV_7500
8. Brain
9. Retina_L and Retina_R
10. Lens_L and Lens_R

Reducing PTV_7500 margins to meet treatment-planning priorities is not generally permissible. In the event that an OAR with higher priority than PTV_7500 is in immediate proximity to PTV_7500 such that dose to the OAR cannot be constrained within Unacceptable Deviation limits, then D95% for PTV_7500 should be lowered to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits. If this approach does not constrain the OAR with higher priority than PTV_7500 within Unacceptable Deviation limits, then D95% for PTV_7500 can be further lowered to below but as close as possible to Variation Acceptable range to ensure that the OAR with higher priority does not exceed Unacceptable Deviation limits; this will be scored as an Unacceptable Deviation for PTV_7500

Dose Distribution Calculations
Dose matrix grid size must be 3mm x 3mm x 3mm or smaller.

Plan Review and Evaluation
- Traditional DVHs and dose distribution displays will be used for plan review and evaluation. DVHs will also be used for retrospective outcome analyses.
- At a minimum, for the non IMPT plans, beam-by-beam review of dose distributions is required to ensure that the bsPTV (or PTV) D95% receives at least 90%.
- While it is understood that DVHs derived from composite dose distribution of all beams have limitations, they are to be used for plan evaluation for comparison of competing plans. Robustness of dose distributions should be evaluated to ensure that the target and critical normal tissue constraints are not violated in the face of set-up and range uncertainties.
- Robustness of PBS or IMPT plans should be evaluated by comparing the nominal dose distribution with simulated setup errors of at least 3mm to ensure that target coverage and critical normal tissue constraints are not too sensitive to setup variations. The range of acceptable variations is left for the individual institution to determine based on their practice and local machine characteristics.

6.8 Patient Specific QA

For photon IMRT plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3mm distance to agreement. For plans with highly modulated dose distributions a 5% dose difference and 3mm distance to agreement criterion may be used. The pass rate should be at least 90% measured for the entire plan.

For all proton plans, patient specific QA is highly recommended. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other similar device. For PBS/IMPT plans, measured dose distribution per field will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3mm distance to agreement. For plans with highly modulated dose distributions a 5% dose difference and 3mm distance to agreement criterion may be used. The pass rate should be at least 90% measured for each field in multiple layers. For passive scattered or uniform scanned beam plans, Gamma analysis is not required but if the plan utilizes a patch field, patient specific QA must be performed with the compensator.

Patient-specific QA data should be kept on record at each institution but will not be centrally collected or reviewed by NRG Oncology.

6.9 Daily Treatment Verification/IGRT

Daily image-guided radiation therapy (IGRT) is required for this protocol, and IGRT credentialing is required as per Section 5.1. The NRG defines IGRT as a computer assisted process. That is, image handling together with calculation of shift and rotations (if available) must be determined with computer assistance. Acceptable systems are: 1) Orthogonal or near-orthogonal 2D imaging that is integrated with the functioning of the delivery device. These systems can use the treatment beam or special kV x-ray head(s) positioned at a known position in the treatment room. 2) A diagnostic quality CT scanner positioned with a known geometry in the treatment room. 3) Volumetric cone-beam devices that use either MV or kV x-ray beam. 4) Tomotherapy technology that uses a fan-beam imaging approach.

For this study, the cranium is used for image registration. It is important to include as much of the anatomy of this structure as possible to ensure correct alignment of the head. **Caution should be taken to avoid excess repeat imaging on a given treatment day to minimize patient dose outside the treatment region, and steps to control patient position to less than 4mm should not be taken.**

6.10 Case Review

These reviews will be ongoing and performed remotely.

NOTE: The 1st 2 patients enrolled by a proton center onto ARM C (PROTON) will require a Pre-Treatment Review. The patient cannot start treatment until they have received approval from IROC- PHL-RT. The Pre-Treatment review process requires 3 business days from the receipt of complete data. See Section 12.2 for specifics.

6.11 Radiation Therapy Adverse Events

6.11.1 Acute

Expected adverse events include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness. Reactions in the ear canals and on the ear should be observed and treated symptomatically; these reactions could result in short-term hearing impairment. Dry mouth or altered taste has been occasionally reported.

6.11.2 Early Delayed

Possible early delayed radiation effects include lethargy and transient worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.

6.11.3 Late Delayed

Possible late delayed effects of radiotherapy include radiation necrosis, leukoencephalopathy, endocrine dysfunction, and radiation-induced neoplasms. In addition, neurocognitive deficits, which could lead to mental slowing and behavioral change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

7.0 DRUG THERAPY (8/7/15)

Protocol treatment must begin on the same day as the first fraction of radiotherapy.

7.1 Temozolomide (2/16/17)

Refer to the package insert for detailed pharmacologic and safety information

7.1.2 Dosing

Temozolomide During Concomitant Radiation Therapy

In all treatment arms, temozolomide will be administered continuously from day 1 of radiotherapy to the last day of radiation at a daily oral dose of 75 mg/m^2 for a maximum of 49 days. The drug will be administered orally daily during radiotherapy, as best tolerated by the patient. During weekends without radiotherapy (Saturday and Sunday), the drug will be taken in the morning.

The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The BSA will be calculated from the height obtained at the pretreatment visit. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be rounded to the nearest 5 mg.

Post-Radiation Temozolomide

In all treatment arms, temozolomide will be administered orally once per day for 5 consecutive days (days 1-5) of a 28-day cycle, for a total of 6 cycles. Patients demonstrating continued benefit from the adjuvant temozolomide can continue treatment to a maximum of 12 cycles. The starting dose for the first cycle will be 150 mg/m^2/day, with a single dose escalation to 200 mg/m^2/day in subsequent cycles if no treatment-related adverse events > grade 2 are noted.

The start of the first cycle will be scheduled 28 days ± 3 days after the last day of radiotherapy. The start of all subsequent cycles (2-12) will be scheduled every 4 weeks (28 days ± 3 days) after the first daily dose of temozolomide of the preceding cycle.

The dose will be determined using the BSA calculated at baseline. The BSA will be re-calculated at the pretreatment visit and if a change in more than 10% in weight has occurred, the dose of temozolomide must be adjusted according to the new BSA. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be rounded to the nearest 5 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.

Prior to each treatment cycle with temozolomide a complete blood count (CBC) will be obtained (within 72 hours prior to dosing). Patients will be instructed to fast at least 2 hours before and 1 hour after temozolomide administration. Water is allowed during the fast period. Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. Treatment should be given at night.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

Antiemetic prophylaxis with a 5-HT$_3$ antagonist is strongly recommended and should be administered 30 to 60 minutes before temozolomide administration.

Patients will be treated with post-radiation temozolomide for 6-12 cycles unless there is evidence of tumor progression (defined in Section 11) or treatment-related toxicity (defined in Section 7.2).

Pneumocystis carinii prophylaxis is **strongly recommended** during the radiation phase (see Section 9.1).

Hepatic toxicity including liver failure has been observed in patients enrolled in clinical studies utilizing temozolomide. In addition, liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. For patients with significant liver dysfunction, the risks and benefits of treatment continuation should be carefully considered.

7.1.3 Administration

Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The capsules should be taken on an empty stomach, therefore a minimum of 2 hours after eating and with no food consumption for at least 1 hour after temozolomide administration.

Antiemetic prophylaxis is usually not required for the continuous daily dosing schedule (during radiation). However, prophylaxis with a 5-HT$_3$ antagonist is recommended prior to administration

of the first few temozolomide doses and should be administered orally 30 to 60 minutes before temozolomide treatment. Most patients report optimal nausea control with the use of a 5-HT_3 antagonist. Routine use of antiemetics is recommended during the adjuvant phase of treatment.

Pneumocystis carinii prophylaxis is **strongly recommended** during the radiation phase (see Section 9.1).

7.1.4 Duration of Temozolomide Treatment

Temozolomide During Concomitant Radiation Therapy

Temozolomide will be administered continuously from day 1 of radiotherapy to the last day of radiation at a daily oral dose of 75 mg/m^2 for a maximum of 49 days. Treatment should be administered continuously, regardless of whether radiotherapy was administered. Missed doses of temozolomide will not be made up at the end of radiotherapy and will be documented in the CRF.

If radiotherapy has to be temporarily interrupted for technical or medical reasons unrelated to the temozolomide administration, then treatment with daily temozolomide should continue. If radiotherapy has to be permanently interrupted then treatment with daily temozolomide should stop. Temozolomide can resume with the initiation of the adjuvant phase of treatment.

Post-Radiation Temozolomide

Temozolomide will be administered orally once per day for 5 consecutive days (days 1-5) of a 28-day cycle, for a total of 6 cycles. Patients demonstrating continued benefit from the adjuvant temozolomide can continue treatment to a maximum of 12 cycles. The start of the first cycle will be scheduled 28 days ± 3 days after the last day of radiotherapy. Missed doses of temozolomide will not be made up.

7.1.5 Supply

Commercial

7.1.6 Other

Prior to starting treatment, the patient will be provided with and instructed in the proper use of a pill diary (see "Pill Diary Template" on the NRG/RTOG website under Non-Study Specific Forms" for an example) or a calendar to record their daily pill consumption. This record will be checked for compliance by the investigator. The diary will be retained in the patient's record for submission to NRG ONLY upon request; i.e., diaries are not to be submitted but will be retained at the site as source documents. Patients who are noncompliant must be re-instructed in the use of the diary.

7.2 Dose Modifications (8/7/15)

Temozolomide During Concomitant Radiation Therapy

No dose reduction will be made, but delay or discontinuation of temozolomide administration will be decided weekly according to hematologic and non-hematologic adverse events (AEs), as specified below.

If the administration of temozolomide has to be interrupted, the radiotherapy will proceed normally. Missed doses of temozolomide will not be made up at the end of radiotherapy. The total number of days and total dose of temozolomide will be recorded on the Treatment Summary Form (TF).

If one or more of the following are observed:

- ANC < 1.0 x 10^9/ L
- Platelet count < 75 x 10^9/L
- Grade 3 treatment-related non-hematologic AE (except nausea and vomiting unless the patient has failed maximal antiemetic therapy, and fatigue)

then treatment with concomitant temozolomide will be withheld until all of the following conditions are met:

- ANC ≥ 1.0 x 10^9/L
- Platelet count ≥ 75 x 10^9/L
- Grade ≤ 1 non-hematologic AE (except nausea and vomiting unless the patient has failed maximal antiemetic therapy, and fatigue)

In case of hematologic AE as defined above, a complete blood count (CBC) should be performed at least twice weekly. In case of non-hematologic AE, the patient should be assessed at least weekly with relevant laboratory test(s). As soon as all of the above conditions are met, the administration of temozolomide will resume at the same dose as used initially.

If one or more of the following are observed:

- ANC < 0.5 x 10^9/L (Grade 4)

- Platelet count < 25 x 10^9/L (Grade 4)
- Grade 4 treatment-related non-hematologic AE (except nausea and vomiting unless the patient has failed maximal antiemetic therapy)

then treatment with concomitant temozolomide should be **stopped**.

Adjuvant treatment can be resumed if hematologic adverse events resolve (platelet > 100 x 10^9/L and ANC > 1.5 x 10^9/L) during the 4-week interval from the completion of chemoradiation to the time for initiation of adjuvant chemotherapy.

If the duration of radiotherapy exceeds 7 weeks, then concomitant treatment with temozolomide should be stopped after 49 days of temozolomide treatment.

Cases of hepatic injury, including fatal hepatic failure, have been observed in patients enrolled in clinical studies utilizing the agent temozolomide. In addition, it was noted that liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. For patients with significant liver function abnormalities, the risks and benefits of treatment continuation should be carefully considered.

Summary of Temozolomide Delay or Discontinuation During Concomitant Radiation Therapy

AE	Value	Grade	Action
ANC	≥ 0.5 and < 1.0 x 10^9/L	3	**Delay** temozolomide until: ---ANC ≥ 1.0 x 10^9/L ---Platelet ≥ 75 x 10^9/L ---Non-hem AE [redacted]
Platelet count	≥ 25 and < 75 x 10^9/L	2, 3	
Non-hematologic (except nausea/vomiting unless the patient has failed maximal antiemetic therapy and fatigue)	NA	3	
ANC	< 0.5 x 10^9/L	4	**Stop** concomitant temozolomide
Platelet count	< 25 x 10^9/L	4	

Non-hematologic (except nausea/vomiting unless the patient has failed maximal antiemetic therapy)	NA	4	

Concomitant temozolomide, if radiotherapy is interrupted
If radiotherapy has to be temporarily interrupted for technical or medical reasons unrelated to the temozolomide administration, then treatment with daily temozolomide should continue. If radiotherapy has to be permanently interrupted then treatment with daily temozolomide should stop. Temozolomide can resume with the initiation of the adjuvant phase of treatment.

Post-Radiation (Adjuvant) Temozolomide
Dosing is based on adverse events (AEs) during the prior treatment cycle. If multiple AEs are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single AE.

Dose Level	Temozolomide Dose, mg/m^2/day	Remarks
-2	100	Reduction if prior AE
-1	125	Reduction if prior AE
0	150	Starting dose cycle 1 (adjuvant)
+1	200	Escalated dose at cycle 2, for cycles 2-12 in absence of AE

Delay
On day 1 of each cycle (within the prior 72 hours), ANC ≥ 1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L and all treatment-related grade 3 or 4 non-hematologic AEs (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) must have resolved (to grade ≤ 1).

If these re-treatment parameters are not met, the treatment will be delayed to a maximum of 4 consecutive weeks. If, after 4 weeks of delay, re-treatment parameters are not met: then any further adjuvant treatment with temozolomide should be stopped.

Dose escalation
If, during the first cycle, all treatment-related non-hematologic AEs observed were grade ≤ 2 (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) and with platelets ≥ 100 x 10^9/L and ANC ≥ 1.5 x10^9/L: then the temozolomide dose should be escalated to dose level 1 and this dose should be used as the starting dose for subsequent cycles. If treatment after cycle 1 has to be delayed because of ongoing non-hematologic AEs of grade ≥ 2, then no escalation is possible. If the dose was not escalated at cycle 2, then the dose should not be escalated in further cycles (3-12).

Dose reductions
If any treatment-related non-hematologic AE observed was grade > 2 (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) and/or if platelets < 50 x 10^9/L and/or ANC < 1 x 10^9/L, then the dose should be reduced by one dose level. For patients who would require dose reductions to a dose level < 100 mg/m^2/day, temozolomide will be stopped. Also, if any of the same non-hematologic grade 3 AE recurs (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) after reduction for that AE, then temozolomide will be stopped.

If any treatment-related non-hematologic AE observed was grade 4 (except nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) then adjuvant temozolomide treatment should be stopped.

- *Subsequent cycles (3-12):* Any dose reductions of temozolomide will be determined according to (1) non-hematologic AE during the preceding treatment cycle, as well as (2) the nadir (lowest/worst) ANC and platelet counts observed. No dose escalation should be attempted. The same dose reductions as for the second cycle should be applied.

- *Important:* If the dose was reduced or delayed for adverse events, there will be no dose escalation.

The reason(s) for dose reduction and/or delay must be documented in the CRF.

Summary of Dose Modification or Discontinuation During Post-Radiation Temozolomide

Worst Non-Hematologic AE (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue**)** **During the Previous Cycles**	
Grade	**Dose Modification**
0-2	No dose modifications for non-hematologic AEs. Dose escalations (only for cycle 2) or reductions based on ANC and platelet counts are applicable.
3	Reduce by one dose level (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable. No further escalation is possible. If the same non-hematologic grade 3 AE recurs (except alopecia, nausea and vomiting) after reduction for that AE, then stop.
4	Stop (except alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue). Dose modifications (escalations or reductions) based on ANC and platelet counts are not applicable.

Nadir Values		**Platelets**		
		≥100 x 10^9/L	**50 – 99 x 10^9/L**	**< 50 x 10^9/L**
ANC	**≥ 1.5 x 10^9/L**	Escalation to DL 1 (cycle 2 only)	Dose unchanged	Reduce by 1 dose level
	≥1 & <1.5 x 10^9/L	Dose unchanged	Dose unchanged	Reduce by 1 dose level
	< 1 x 10^9/L	Reduce by 1 dose level	Reduce by 1 dose level	Reduce by 1 dose level

Note: A complete blood count must be performed 21 days (± 48 hours) after the first daily dose of each adjuvant treatment cycle.

Hematologic AE on Day 1 of Each Cycle (within 72 hours before)	
AE	**Delay**
ANC< 1.5 x 10^9/L and/or Platelet count < 100 x 10^9/L	Delay up to 4 weeks until all resolved. If unresolved after 4 weeks then stop. If resolved, dose delay/reductions based on non-hematologic AEs are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

Non-Hematological AE (except for alopecia, nausea and vomiting unless the patient has failed maximal antiemetic therapy and fatigue) on Day 1 of Each Cycle (within 72 hours before)	
Grade	**Delay**
2-3	Delay up to 4 weeks until all resolved (to grade ≤ 1). If unresolved after 4 weeks, then stop. If resolved, dose delay/reductions based on ANC and platelets are applicable. If treatment has to be delayed for AEs, then no escalation is possible.

7.3 Modality Review

The Medical Oncology Co-Chair, Antonio Omuro, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Unacceptable Deviation, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

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

7.4 Adverse Events

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP Adverse Event Reporting System (CTEP-AERS) application accessed via either the CTEP web site https://eapps-ctep.nci.nih.gov/clm/login.htm?destinationURL=https%3A%2F%2Feapps-ctep.nci.nih.gov%3A443%2Fctepaers%2Fpublic%2Flogin.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.4.1 Adverse Events (AEs)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

7.4.2 **Serious Adverse Events (SAEs)** — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.5 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.5, CTEP-AERS Expedited Reporting Requirements . **Contact the CTEP-AERS Help Desk if assistance is required.**

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

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

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

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

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

Secondary Malignancy

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

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

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

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

Second Malignancy

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

7.5 **CTEP-AERS Expedited Reporting Requirements**

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via accessed via the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

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

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS -24 Hour Notification requires that an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to the NRG dedicated SAE FAX, 215-717-0990.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS as "expedited reporting NOT required" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT Required" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 2 and 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1).

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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

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

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

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

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

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes

Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days		24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	10 Calendar Days	

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

Expedited AE reporting timelines are defined as:

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

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

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

- ☐ All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- ☐ Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- ☐ Grade 3 adverse events

Effective Date: May 5, 2011

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3

The following are protocol-specific inclusions to expedited reporting via CTEP-AERS. Report the following AEs in an expedited manner regardless if they meet the reporting criteria outlined in the above table: radiation necrosis (***all*** grades).

The following are protocol specific exceptions to expedited reporting via CTEP-AERS. Report the following AEs in an expedited manner only if they **exceed** the grade in parentheses next to the AE: vomiting (gr.3), nausea (gr.3). Routine adverse event reporting on the case report form fulfills safety reporting requirements for these events at the aforementioned grades.

8.0 SURGERY

Not applicable

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy (8/7/15)

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

9.1.1 Anticonvulsants: Anticonvulsants may be used as clinically indicated. The regimen and dosing schedule at study entry and any subsequent changes in the anticonvulsant regimen and/or dosing schedule must be recorded. EIAED use does NOT change dosing of temozolomide.

9.1.2 Corticosteroids: Corticosteroids may be administered at the treating physician's discretion. Doses at study entry must be recorded per Appendix I. The goal is to use the lowest clinically necessary dose of corticosteroids.

9.1.3 Antiemetics: Prophylactic antiemetics may be administered at the treating physician's discretion. Guidelines for antiemetic prophylaxis with a 5-HT_3 antagonist are specified in Sections 7.1.2 and 7.1.3 .

9.1.4 Pneumocystis Carinii Prophylaxis:
Both corticosteroid therapy and continuous temozolomide therapy induce lymphopenia. Patients receiving any of these drugs or both concomitantly are at an increased risk for opportunistic infections.

Therefore, prophylaxis against *P. carinii* pneumonia is strongly recommended for all patients receiving temozolomide during radiotherapy: trimethoprim-sulfamethoxazole (Bactrim forte®, Bactrim DS®) 1 tablet 3 times per week or monthly pentamidine inhalations (300 mg via aerosol monthly) or dapsone 100 mg po each day (except in patients with G6-PD deficiency). Prophylaxis is strongly recommended to continue for the duration of radiotherapy, regardless of the lymphocyte count.

In addition, daily temozolomide has been associated with selective CD4 lymphopenia (Su, Sohn, et al., 2014). Throughout chemoradiotherapy, it is strongly recommended that all patients have CD4 quantification prior to initiation of chemoradiotherapy, at 4 weeks during chemoradiotherapy, and at completion of chemoradiotherapy. If the CD4 is < 200 prior to or during chemoradiotherapy, then *P. carinii* prophylaxis is required and the CD4 must be monitored every 2 weeks until CD4 is > 200. If the lymphocyte count is ≥ 500 or the CD4 is > 200, then *P. carinii* prophylaxis is strongly recommended but not mandatory.

During the adjuvant chemotherapy phase, it is strongly recommended that CD4 quantification is obtained at day 1 of each cycle. In addition, CD4 quantification is mandatory if **lymphocyte count < 500/mm3.** If the CD4 is ≤ 200, then *P. carinii* prophylaxis is recommended to continue and the CD4 is required to be quantified every 2 weeks until CD4 is > 200, at which point *P. carinii* prophylaxis can be stopped. If the lymphocyte count is ≥ 500 or the CD4 is > 200, then prophylaxis and CD4 quantification are no longer mandatory.

See Appendix I for further details regarding scheduling CD4 quantification.

9.2 Non-Permitted Supportive Therapy

9.2.1 Growth factors are not permitted to induce elevations in neutrophil count for the purposes of: (1) administration of temozolomide on the scheduled dosing interval; (2) allowing treatment with temozolomide at a higher dose; or (3) avoiding interruption of the treatment during concomitant radiotherapy.

9.2.2 No other investigational drugs will be allowed.

9.2.3 Surgical procedures for tumor debulking, other types of chemotherapy, and immunotherapy or biologic therapy must not be used. Further, additional stereotactic boost radiotherapy is not allowed. All further therapy is at the treating physicians discretion, but should be recorded in the CRF.

9.2.4 Carmustine wafers or any form of brachytherapy is not permitted prior to study entry or while the patient is on study.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission.

If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank at San Francisco acquires and maintains high quality specimens from NRG trials. Tissue from each block is preserved through careful block storage and processing. The NRG encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The NRG Oncology Biospecimen Bank also collects tissue for Central Review of pathology. Central Review of tissue can be for eligibility and/or analysis

In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of central review of pathology (mandatory for eligibility) and tissue banking for future translational research (strongly recommended). [For patients who have consented to participate in the banking component of the study, see sample informed consent.]

10.2 Specimen Collection for Central Review (Mandatory) (2/16/17)

To be eligible for this study, the patient must have a GBM, WHO grade IV. Features of a high-grade astrocytic neoplasm with tumor necrosis and/or microvascular proliferation must be present.

MGMT testing will be performed centrally at the CLIA-certified MD Anderson Cancer Center Molecular Diagnostics Lab (MDACC-MDL)".

MGMT testing performed on bisulfite-converted DNA extracted from the FFPE tissue block. MGMT methylation status will be determined by quantitative, methylation-specific real-time PCR using primers that detect 9 CpG sites with the MGMT promotor, located within an enhancer region in the first intron and identical to those evaluated in EORTC 26981/22981, National Cancer Institute of Canada (NCIC) CE3 trial, which showed that this epigenetic variation predicted for improved survival (Hegi, Diserens et al. 2005). Residual material will be used to assay additional methylation sites using a secondary analysis platform (Illumina *Infinitum* MethylationEPIC Bead Chip arrays) that provides information on *MGMT* promoter status as well as other methylation sites that may prove to be similarly related to patient outcome. This method offers the potential to reduce the amount of tissue required for molecular stratification in future clinical trials. Funding for this work is provided by NIH NCI SPORE grant P50 CA127001. A detailed description of the assay can be found in Appendix X.

For sites able to assess MGMT locally by LabCorp or MDACC-MDL, tissue for central pathology review and official LabCorp or MDACC-MDL result must be received at the NRG Oncology Biospecimen Bank San Francisco on or before postoperative calendar day 40. Tumor tissue will then be used for central pathology review, and the site's local MGMT report from LabCorp or MDACC-MDL will be used to stratify the patient. . If stratification was based on a LabCorp result, central review of MGMT will be performed post-stratification at the MDACC-MDL, but Step 2 registration and protocol treatment can proceed without central review of MGMT.

For sites not able to assess MGMT locally by LabCorp or MDACC-MDL, tumor tissue must be received at the NRG Oncology Biospecimen bank on or before postoperative calendar day 30. Tumor tissue will then be used for central pathology review and for central MGMT analysis at the MDACC-MDL. The MDACC-MDL central MGMT result will be used to stratify the patient, after which Step 2 registration and protocol treatment can proceed. If tumor tissue is not received on or before postoperative calendar day 30, then the patient may NOT enroll on this trial, as central pathology review will not be complete in time for the patient to start treatment within 49 days following surgery.

10.2.1 The following materials will be required for tissue evaluation:

- Representative tissue blocks with corresponding H&E slide(s) that contain diagnostic viable tumor. As a guide, at least 1 cubic centimeter of tissue composed primarily of tumor must be present. Note that the tissue blocks composed primarily of either normal tissue or necrotic tissue are inadequate for molecular analysis, as it depends on the presence of viable tumor tissue. In cases where a single block has insufficient tumor, tissue for multiple blocks can be combined to ensure specimen adequacy. If Dr Aldape determines that the block that was sent is insufficient, he will contact the site in an attempt to obtain additional tissue which could render the patient eligible, *provided there is sufficient time prior to randomization*. Given the narrow time frame for patient evaluation, *submission of at least 2 blocks is highly encouraged and recommended to maximize the chances of having sufficient tissue for central review for eligibility*. One or both blocks will be returned upon request. Examples of adequate and inadequate samples are shown below

Examples of inadequate (*left*) and adequate (*right*) tissue samples for study entry. In both cases a slide was cut from the submitted block and stained with H&E. Even though the slide on the left had tissue diagnostic of glioblastoma, the amount of tumor will be insufficient for molecular testing

- An accompanying H&E from the same block(s) is **mandatory** for rapid diagnosis. The H&E(s) can be a recut from the block, it does not have to be the diagnostic H&E. Dr. Aldape can only review blocks with matching H&E slides. H&E slides will remain at the bank as part of the central review files for patients randomized to treatment. Slides will be returned to the submitting institution for patients not randomized to treatment.
  - **Required Paperwork: ST, P4 forms and pathology report** must be included with the pathology shipment and must include the NRG protocol number, patient case number, patient's initials, and NRG institution number and name. Specimen Transmittal Form listing pathology materials being submitted for Central Tissue Evaluation
  - Pre-Randomization Pathology Submission Form (P4) must be completed by the local pathologist. Include on the P4 form the name, telephone number, email, and fax number of the person to notify with the results of the tissue evaluation.
  - Pathology Report documenting that the submitted material contains tumor; the report must include the NRG protocol number, patient case number, and the patient's initials. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- Tissue evaluation will be required for every case. Dr. Aldape will review these materials via digital remote review from Toronto General Hospital. See protocol cover page for additional contact information.
- .

Ship pathology material submissions Monday-Friday by overnight courier (to:

NRG Oncology Biospecimen Bank San Francisco
2340 Sutter St, room S341
UCSF
San Francisco, CA 94115
415-476-7864/ fax 415-476-5271/ emailNRGBB@ucsf.edu

- Use priority overnight Fed Ex or UPS. Do NOT ship by "first overnight" or "Saturday" delivery as the lab is closed before 8am, weekends and holidays.
- Notify the Biobank (**NRGBB@ucsf.edu**) and Dr. Aldape (**kaldape@gmail.com**) by email (please use both email addresses) on or before the day of submission: (1) that a case is being submitted for review; (2) the name of the contact person; (3) when to expect the sample; and (4) the overnight shipping carrier and tracking number.
- **If Dr. Aldape is given the proper email notification, central review of histology and evaluation of tissue adequacy is guaranteed within 3 business days of receipt of the H&E slide, tumor block and required paperwork.**
- Dr. Aldape will submit electronically the results of his review (P4 form) into the NRG database. An email notification about central pathology review results will be sent to the site when the P4 form is on file. If the patient is deemed eligible per pathology results, the site will be able to proceed to step 2 to proceed to step 2 registration only ***after*** MGMT results have been completed ***and*** the site has been notified by Headquarters. If there is any tissue related-issue (e.g. not enough tissue), Dr. Aldape or the biospecimen bank will contact the site.
- Since there is a narrow time window within which the review must be completed, submission of H& E and tumor blocks should be done as soon as possible to ensure sufficient time for review. *The Biospecimen Bank must receive the H&E and tumor block within **30 days** of surgery, to allow time for review and molecular testing. Samples received after this time cannot be accepted in most cases. See section 10.2 for detailed timing/testing requirements*
- If the patient does not meet eligibility requirements, *all* tissue and forms will be returned to the participating submitting institution. The site must complete a tissue return request form and provide a return airbill

10.2.2 After confirming histopathologic diagnosis, the Biospecimen Bank will cut sections for DNA isolation and will send the tissue to MDACC-MDL for MGMT methylation analysis.

For sites able to assess MGMT locally by LabCorp or MDACC-MDL, the site must submit the LabCorp or MDACC-MDL MGMT report such that it is received by the NRG Biospecimen Bank on or before postoperative calendar day 40. NRG Oncology will use this report to stratify the patient.

For sites not able to assess MGMT locally by LabCorp or MDACC-MDL, if tissue is received on or before postoperative calendar day 30, central MGMT results from MDACC-MDL will be conveyed to NRG Headquarters for patient stratification and randomization within 10 business days after the Biospcimen Bank receives the tumor block as detailed above. If tumor tissue is not received on or before postoperative calendar day 30, then the patient may NOT enroll on this trial, as central pathology review will not be complete in time for the patient to start treatment within 49 days following surgery.

10.2.3 When MDACC-MDL has completed the MGMT methylation test tissue of consenting patients will be banked at the NRG Oncology Biospecimen Bank (see Section 10.3). If the submitting institution requests the block to be returned then the Biospecimen Bank will punch the block with one to two 2-3 mm punches for banking for consenting patients and will return the remaining tissue to the submitting institution. The submitting institution must provide an airbill for the return.

10.3 Specimen Collection for Tissue Banking and Translational Research (recommended but not required) (8/7/15)

10.3.1 FFPE tissue, frozen tissue, blood, and urine will be banked for future research for consenting patients, as outlined in the Specimen Collection Summary table. FFPE Punch kits, Blood, Urine and Frozen Tissue Collection kits can be requested by email from the NRG Oncology Biospecimen Bank at **NRGBB@ucsf.edu** . Frozen Tissue kits will only be shipped if specifically requested.

10.3.2 Submission Guidelines

The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the NRG protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80°C, must be included.

10.3.3 Storage Conditions

Store frozen specimens at -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on the ST Form the storage conditions used and time stored.

10.3.4 Submit materials for banking for future research as follows (NOTE: Central review FFPE samples must be shipped as detailed in Section 10.2)

Courier Address (FedEx, UPS, etc.): For Trackable FFPE and ALL Frozen Specimens
NRG Oncology Biospecimen Bank San Francisco
2340 Sutter Street, Room S341
University of California San Francisco
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.4 Specimen Collection Summary (2/16/17)

Specimens for Mandatory Central Review **Note: If MGMT can be assessed locally by LabCorp or MDACC-MDL, then the official LabCorp or MDACC-MDL result must also be received at the time of tissue submission on or before postoperative day 40.**			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide(s) MUST be from the same block(s) being submitted. Can be a recut, does not have to be the diagnostic slide	Slide shipped ambient via overnight carrier.
1-2 paraffin-embedded tissue blocks of the primary tumor taken before initiation of treatment	Pre-treatment	1-2 Paraffin-embedded tissue blocks (must match the H&E slide(s) being submitted)	Block shipped ambient. Use cold packs during warm weather.

Specimens for Assaying Additional Methylation Sites **(For patients who consent to the use of residual material for this purpose)** Residual material will be used to assay additional methylation sites using a secondary analysis platform (Illumina *Infinitum* MethylationEPIC Bead Chip arrays) that provides information on *MGMT* promoter status as well as other methylation sites that may prove to be similarly related to patient outcome. This method offers the potential to reduce the amount of tissue required for molecular stratification in future clinical trials. Funding for this work is provided by NIH NCI SPORE grant P50 CA127001.			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Residual material after mandatory central review occurs (per above)	N/A	N/A
1-2 paraffin-embedded tissue blocks of the primary tumor taken before initiation of treatment	Residual material after mandatory central review occurs (per above)	N/A	N/A

Specimens for Banking for Future Research (For patients who consent to biobanking for future research)			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide(s) Note: Can be same slide as submitted above for central review.	Slide shipped ambient via overnight carrier
1-2 paraffin-embedded tissue blocks of the primary tumor taken before initiation of treatment or one-two 2-3 mm diameter core of tissue punched from the tissue block with a punch tool.	Pre-treatment	1-2 Paraffin-embedded tissue blocks or 1-2 two-three mm punches from the blocks (must match the H&E slide(s) being submitted) Note: Can be same block as submitted above for central review, or punches from the block	Block or punch shipped ambient. Use cold packs during warm weather.
Frozen Tumor Tissue block if available	Pre-treatment	Frozen tumor tissue	Frozen Tissue sent on dry ice via overnight carrier.
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Within 28 days prior to treatment	Frozen serum samples containing a minimum of **0.5 mL** per aliquot in 1 mL cryovials (five)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Within 28 days prior to treatment	Frozen plasma samples containing a minimum of **0.5 mL** per aliquot in 1 mL cryovials (five)	Plasma sent frozen on dry ice via overnight carrier
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Within 28 days prior to treatment Note: If site missed this collection time point site may collect whole blood for DNA at a later time point instead but must note this on the ST Form.	Frozen whole blood samples containing **1 mL** per aliquot in 1ml cryovials (three)	Whole blood sent frozen on dry ice via overnight carrier
10-20 mL clean-catch urine	Within 28 days prior to-treatment	**5-10 mL** urine aliquots in 1-2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20°C or -80°C	Urine sent frozen on dry ice via overnight carrier

10.5 Reimbursement

Please note that with the start of the new NCI National Clinical Trials Network (NCTN) Program, NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system. OPEN will serve as the registration system for all patient enrollments onto NCI-sponsored NCTN trials, including this study, which will be transitioned into the new Program from the NCI-sponsored Cooperative Group Clinical Trials Program.

10.6 Confidentiality/Storage

(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.6.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.6.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

See Appendix I

11.2 CD4 Lymphocyte Count

Throughout chemoradiotherapy, it is strongly recommended that all patients have CD4 quantification prior to initiation of chemoradiotherapy, at 4 weeks during chemoradiotherapy, and at completion of chemoradiotherapy. CD4 lymphocyte counts will be assessed locally and will be used to determine medical need for *P. carinii* prophylaxis. In addition, results will be submitted as part of follow-up data forms to prospectively compare CD4 lymphopenia between treatment arms and determine whether CD4 lymphopenia impacts overall survival.

Technique for measuring CD4 cell counts will be left to the local institution, but to ensure accuracy of CD4 lymphocyte quantification, it is important to use the same method of measurement throughout all of the assessments. For example, it would not be appropriate to measure baseline CD4 count using standard flow cytometry while measuring subsequent CD4 counts with alternative systems not using flow cytometry.

See Section 9.1 for further details regarding how CD4 lymphocyte counts will be used to determine medical need for *P. carinii* prophylaxis.

See Appendix I for further details regarding scheduling CD4 quantification.

11.3 Net Clinical Benefit Assessments (10/6/14)

NOTE: Sites must offer English-speaking patients the opportunity to participate in this component of the study.

Symptom Burden (**Translations Not Available for This Protocol; enrollment to Net Clinical Benefit restricted to English-speaking participants)**

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

interfered with different aspects of the patient's life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0-10 scales.

Neurocognitive Function (**Translations Not Available for This Protocol; enrollment to Net Clinical Benefit restricted to English-speaking participants)**
Neurocognitive function will be assessed using the Hopkins Verbal Learning Test – Revised (Benedict 1998), Trail Making Test (Tombaugh 2004), and the Controlled Oral Word Association test (Ruff 1996). These tests were selected because they are widely used and standardized psychometric instruments that have been shown to be sensitive to the impact of cancer and the neurotoxic effects of cancer treatment in other clinical trials (Gilbert 2014; Meyers 2004; Wefel 2011). The tests have published normative data that take into account age and, where appropriate, education and gender. The tests must be administered by a healthcare professional (eg, psychologist, physician, research associate, nurse) who is pre-certified by Dr. Wefel (see Section 5).

11.4 MRI Review (8/7/15)
Response assessment will be determined locally using the MacDonald criteria. The serial CT/MRI will be examined at the institution by an independent reviewer (i.e., a radiologist who is not involved in the patient's care). The evaluation of the scans will be compared to and correlated with the patient's clinical course.

To ensure accuracy of measuring progression, it is important to use the same method of assessment from one scan to the subsequent scans. For example, it would not be appropriate to compare a pre-treatment non-contrast brain MRI on a 0.5T scanner with 0.5 cm slice thickness to a post-treatment double-gadolinium enhanced MRI on a 3T scanner with 0.2 cm slice thickness.

11.5 Advanced Imaging (8/7/15)

Advanced MRI scans will be obtained at baseline and at subsequent follow-up time-points at designated, pre-approved sites on subjects consented and enrolled into the advanced imaging component. See Appendix VIII regarding site qualification.

Advanced MRI Image Acquisition
Advanced MR imaging sequences include MR FLAIR, contrast-enhanced T1-weighted, DWI and DSC See Appendix VIII for further details.

Advanced MRI Imaging Schedule: MR FLAIR, contrast-enhanced T1-weighted, standardized dynamic susceptibility contrast (DSC) and diffusion weighted imaging (DWI) will be obtained at 4 time points corresponding to baseline prior to the start of radiation treatment, Week 3 during chemoradiation, and at subsequent clinical follow-up prior to D1 of cycle 1 and 4 (See Appendix I).

Advanced MRIs obtained at designated, pre-approved sites on subjects consented and enrolled into the advanced imaging component will be collected for central review. Central MR review will occur at batched readings following completion of study enrollment. Imaging will be anonymized, submitted and transferred to analysis workstations using ACR TRIAD software. Advanced MR imaging will be analyzed retrospectively using histogram and quantitative analyses.

The exploratory aim will evaluate MR diffusion and perfusion imaging to differentiate between tumor progression and pseudo-progression based on early changes in relative cerebral blood volume (rCBV) leakage corrected and apparent diffusion coefficient (ADC) in comparison to standard MR imaging response assessments such as MacDonald criteria. These data will provide important information confirming the clinical use of a standardized DSC imaging protocol in a

large, multi-institutional prospective study to differentiate tumor progression from true tumor progression and identify early, imaging biomarkers of response and survival.

11.6 Measurement/Definition of Progression/Recurrence

Response will also be evaluated in this study using the international criteria proposed by Macdonald et al. (1990)

11.6.1 *Complete Response **(CR)***: Requires all of the following: complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically.

11.6.2 *Partial Response **(PR)***: Requires all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measureable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically.

11.6.3 *Stable Disease **(SD)***: Requires all of the following: does not qualify for complete response, partial response or progression; and stable clinically.

11.6.5 *Progression **(P)***: Defined by any of the following: ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration.

However, it should be noted that following radiotherapy and concomitant temozolomide, up to 50% of patients with glioblastoma may present with increase in tumor size and/or edema as a reaction to treatment, mimicking tumor progression. This condition has been referred to as *tumor pseudoprogression*, and may abate over time, which distinguishes it from real progression of disease. It is more frequent in patients with methylated MGMT promoter. The increased radiotherapy doses used in the trial may enhance this effect. Moreover, rates of radionecrosis are expected to increase in this trial given the radiotherapy dose-escalation.

When pseudoprogression or radionecrosis are suspected, all efforts should be made to further document the event and differentiate it from real tumor progression. Surgical resection or biopsy for histological confirmation, whenever feasible, is strongly encouraged. Alternative imaging methods, such as MR perfusion and FDG-PET scan, may also provide additional helpful information.

At the discretion of the treating physician, patients with suspected or confirmed tumor pseudoprogression or radionecrosis may remain on temozolomide treatment. If, at any time, a patient enrolled on this study undergoes a neurosurgical procedure (i.e., for the differentiation of pseudoprogression versus tumor progression, or for tumor debulking in suspected recurrent tumor or radionecrosis), results of pathology evaluation will be collected. If real tumor progression is histologically confirmed, the date of progression should be the date of the scan that first showed the increase in tumor size prior to the procedure.

After patients are removed from study for reasons other than withdrawal of consent, patients should continue to be followed for survival and for the development of late radiotherapy effects until the patient's death or for the duration of the study.

11.7 Criteria for Evaluation of Therapy Effectiveness

11.7.1 Overall survival will be measured from the date of randomization to the date of death or, otherwise, the last follow-up date on which the patient was reported alive

11.7.2 Progression-free survival will be measured from the date of randomization to the date of progression (as reported by the institution), death, or, otherwise, the last follow-up date on which the patient was reported alive.

11.7.3 The quality of survival will be measured by neurological functional classification and performance status.

11.7.4 Toxicities will be measured using the CTCAE criteria, version 4.0.

11.8 Criteria for Discontinuation of Protocol Treatment (8/7/15)

☐ Progression of disease during the protocol

- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flowsheet, and NRG Headquarters data management must be notified;
- A delay in drug therapy > 4 weeks for temozolomide as described in Section 7.
- The patient may withdraw from the study at any time for any reason. The institution must notify NRG Headquarters Data Management about this in writing.

If protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION

If you are a proton center partnering with a photon center, you will be responsible for the overall data submission into the Medidata Rave and TRIAD. However, due to strict SAE reporting time constraints, each site will be responsible for reporting SAEs in CTEP-AERS. The photon center must copy the proton Site RA and PI when submitting the AERS report in CTEP-AERS.

12.1 Summary of Data Submission (2/16/17)

Folder	Form/Item
Registration via the OPEN System	***Subject Enrollment***
Enrollment When pushed into RAVE there will be 5 forms representing registration	***Demography*** ***Step Information*** ***Treatment Assignment*** ***Eligibility Checklist*** ***Eligibility Checklist II***
CD4 Count: See Appendix I for time points	***CD4 Lab Results***
Baseline	****History and Physical*** ****KPS and Neurologic Function*** ****Pathology Report*** *(uploaded by sites)* ****Pathology Form*** *(P4 form not visible to sites in RAVE but results of central review emailed to sites by the central reviewer)* ****Tumor Work-up*** ***Patient History*** *(formerly known as the A5)* ***Any Anticonvulsant?*** ***Conmedication Anticonvulsants*** *– if Has the dose of anticonvulsant changed during* this reporting period? = 'yes' ***Any Corticosteroid****?* ***Conmedication Corticosteroids*** *– if Is the* patient receiving corticosteroids? = 'yes' ****Baseline Lab Results*** ***SOC Imaging*** ***MRI Image Transmittal Worksheet*** *(consenting patients)* ***Internal Imaging QC*** *(consenting patients)* *Report data assessed prior to registration
RT Plan Upload	***Digital Data*** *(Upload of e-mail confirmation of the DDSI form when the TRIAD*

	submission required is complete)
Concurrent Treatment	☐ ***RT Administration*** (*with* ***RT Treatment Chart Upload*** embedded on that form) ☐ ***RT Treatment*** – *if Was radiation therapy* given? = 'yes' ☐ ***Protocol Specific RT Questions*** – if Did the patient receive radiation therapy? = 'yes' ☐ ***Temozolomide*** ☐ ***Was Tumor Response Evaluated?*** ☐ ***Disease Assessment (McDonald)*** – *if* Was Tumor Response Evaluated? = 'yes' ☐ ***Any Adverse events?*** ☐ ***Adverse Events*** – *if Any Adverse Events?* = 'yes' ☐ ***MRI Image Transmittal Worksheet*** *(consenting patients)* ☐ ***Internal Imaging QC*** *(consenting patients)*
Concurrent Labs	☐ ***Labs_Week 2, 4, 6***
Adjuvant Treatment: 13 folders **Pre-cycle 1**** **Cycle 1** **Cycle 2** **Cycle 3** **Cycle 4** **Cycle 5** **Cycle 6** **Cycle 7** **Cycle 8** **Cycle 9** **Cycle 10** **Cycle 11** **Cycle 12**	☐ ***History and Physical*** ☐ ***KPS and Neurologic Function*** ☐ ****Temozolomide*** ☐ ***Was Tumor Response Evaluated?*** ☐ ***Disease Assessment (McDonald)*** – *if* Was Tumor Response Evaluated? = 'yes' (required prior to cycle 1, 4,7,10 and end of cycle 12 if treatment administered) ☐ ***Any adverse Events?*** ☐ ***Adverse Events*** – *if Any adverse events?* = 'yes' ☐ ***Any Anticonvulsant?*** ☐ ***Conmedication Anticonvulsants*** – *if Has the dose of anticonvulsant changed during* this reporting period? = 'yes' ☐ ***Any Corticosteroid****?* ☐ ***Conmedication Corticosteroids*** – *if Is the* patient receiving corticosteroids? = 'yes' ☐ ***Any Labs?*** ☐ ***Lab Results*** – if Any Labs? = 'yes' ☐ *****SOC Imaging*** *(within 7 days prior to start of cycle 1 and cycle 4)* ☐ ***MRI Image Transmittal Worksheet*** *(consenting patients)**** ☐ ***Internal Imaging QC*** *(consenting patients)**** *Not included in Pre-cycle 1 folder *** Pre-cycle 1 and cycle 3 folders only
Year 1: Follow-up every 3 months=4 folders **3 Month Follow-up** **6 Month Follow-up** **9 Month Follow-up** **12 Month Follow-up**	☐ ***Patient contacted*** ☐ ***History and Physical*** – if *Patient able to* be contacted? = 'yes' ☐ ***KPS and Neurologic Function***– if *Patient* able to be contacted? = 'yes' ☐ ***Follow-up*** – *if Patient able to be*

Year 2: Follow-up every 4 months=3 folders **16 Month Follow-up** **20 Month Follow-up** **24 Month Follow-up** **Year 3 and up**: Follow-up every 6 months **30 Month Follow-up** **36 Month Follow-up** **42 Month Follow-up** **48 Month Follow-up** **54 Month Follow-up** **60 Month Follow-up** ….	contacted? = 'yes' ☐ ***Primary Cause of Death*** *– if Vital Status =* 'dead' ☐ ***Disease Assessment*** *– if Documented* clinical assessment? = 'yes' ☐ ***New Primary Cancer*** *– if New Primary* cancer? = 'yes' ☐ ***Non-Protocol Treatment*** *– if Non-protocol* cancer therapy? = 'yes' ☐ ***Non-Protocol Surgery*** *– if Non-protocol* cancer therapy type = 'surgery' ☐ ***Any adverse Events?*** ☐ ***Adverse Events*** *– if Any adverse events?* = 'yes' ☐ ***Any Anticonvulsant?*** ☐ ***Conmedication Anticonvulsants*** *– if Has the dose of anticonvulsant changed during* this reporting period? = 'yes' ☐ ***Any Corticosteroid****?* ☐ ***Conmedication Corticosteroids*** *– if Is the* patient receiving corticosteroids? = 'yes'
CTEP-AERS	☐ ***CTEP-AERS Upload Form*** *– used by HQ to upload CTEP-AERS reports, sites have read only access to this folder/form*
Source Documentation Upload	☐ ***Source Documentation Upload*** *– used by sites in the event that source doc. needs to be uploaded to HQ*
Net Clinical Benefit (NCB) Coversheets will appear in the following folders if the patient has consented to the NCB component and must be completed regardless of progression or discontinuation of treatment: ☐ **Baseline** ☐ **Cycle 3** (Adjuvant Treatment, prior to cycle 4) ☐ **Cycle 12** (Adjuvant Treatment, end of cycle 12)	☐ ***MDASI Coversheet*** ☐ ***MDASI-BT**** ☐ ***Neurocognitive Function Coversheet (HVLT-R, TMT Part A and Part B, COWA)***** ☐ ***Education Form****** **MDASI-BT form only appears if the corresponding* coversheet is submitted and "Was the patient questionnaire completed?" was answered as YES. ***Only one coversheet will need to be completed for all the neurocognitive testing.* ****Education form only appears once in the Baseline folder.*
Advanced Imaging forms will appear in the following folders if the patient has consented to the Advanced Imaging component and must be completed regardless of progression or discontinuation of treatment: • **Baseline** • **Concurrent Treatment** • **Pre-cycle 1** • **Cycle 3**	☐ ***MRI Image Transmittal Worksheet (to be filled out by site)*** ☐ ***Internal Imaging QC (to be filled out by ACR Imaging Core Lab Tech)***

12.2 Summary of Dosimetry Digital Data Submission

Item	Due
Preliminary Dosimetry Information **NOTE: 1st 2 cases on PROTON Arm require Pre-Treatment reviews** **Digital data submission includes the following**:	Within 1 week of start of RT
Arm A1 and Arm A2 DICOM Items: ☐ DICOM CT Image ☐ DICOM Post-Op MR ENTIRE Post-Op Series must be submitted See the note below ☐ DICOM Structure ☐ DICOM Dose –Initial ☐ DICOM Dose – Boost ☐ DICOM Dose - Composite ☐ DICOM RT Plan - Initial ☐ DICOM RT Plan – Boost DVH Analysis Worksheet Digital Data transmission Form	Within 1 week of start of RT
Arm B and Arm C DICOM Items: ☐ DICOM CT Image ☐ DICOM Post-Op MR ENTIRE Post-Op Series must be submitted See the note below ☐ DICOM Structure ☐ DICOM Dose ☐ DICOM RT Plan DVH Analysis worksheet Digital Data transmission Form	Within 1 week of start of RT

Completed Data sheet (DV) available on the RTOG Website submitted via TRIAD

The complete Post- Op MRI series via TRIAD submitted at the same time as the plan above. NOTE: if an additional scan was performed for planning purposes it to must be submitted as a complete series along with the CT plan

Upon submission of the digital data Via TRIAD, complete an online digital data transmission form (DDSI) located on the website at
http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx

12.3 Summary of MRI Digital Data Submission (outlined in Appendix VIII) (8/7/15)

Item	Due
MRI exams per the imaging guidelines outlined in Appendix VIII will be submitted to IROC DI - Philadelphia using ACR TRIAD v4x or higher software. For questions regarding the advanced imaging contact imagearchive@acr.org. In the subject line enter: "IROC-NRG BN001 advanced imaging" TRIAD will be the sole means of image transfer to the IROC Core Laboratory. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging. Information and instructions for download and installation of TRIAD software is available at http://triadhelp.acr.org/ under "Clinical Trials". Staff submitting imaging must first be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.	
Advanced MR Image submission for IROC via TRIAD (see above)	*(inclusive of Standard of Care MRI series)*
DICOM MRI Exam (Complete diagnostic standard of care *plus Advanced Imaging*)	Baseline
DICOM MRI Exam (Complete diagnostic research MR scan)	Week 3 mid-course during RT
DICOM MRI Exam (Complete diagnostic standard of care *plus Advanced Imaging*)	Pre-Cycle 1 Chemo
DICOM MRI Exam (Complete diagnostic standard of *care plus Advanced Imaging*)	Pre-Cycle 4 Chemo

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

Overall survival (failure defined as death due to any cause) compared between dose-escalated and –intensified photon IMRT or proton beam therapy with concomitant and adjuvant temozolomide and standard-dose photon irradiation with concomitant and adjuvant temozolomide

13.2 Secondary Endpoints (8/7/15)

13.2.1 Overall survival to compare dose-escalated and –intensified photon IMRT to dose-escalated and –intensified proton beam therapy
13.2.2 Progression-free survival
13.2.3 Treatment-related toxicity, as measured by the CTCAE v4
13.2.4 Instrumental variable analysis
13.2.5 Perceived cognitive function, as measured by MDASI-BT
13.2.6 Neurocognitive function, as measured by HVLT-R, TMT A, TMT B, and COWA
13.2.7 CD4 lymphopenia
13.2.8 Use of MR diffusion and perfusion imaging to differentiate between tumor progression and pseudoprogression
13.2.9 Use of Week 3 MR diffusion and perfusion imaging as early predictors of overall survival

13.3 Sample Size and Power Justification

13.3.1 Treatment Comparison

This study is designed as a randomized phase II trial with 2 groups. In Group I (photon IMRT centers), patients will be randomized to either conventional photon irradiation with concomitant and adjuvant temozolomide (control arm A1) or dose-escalated and -intensified photon IMRT with concomitant and adjuvant temozolomide (experimental arm B). It is assumed that median overall survival (starting from randomization) for control arm A1 is 16 months. It is hypothesized that experimental arm B will lead to median overall survival of 22.2 months, corresponding to a hazard ratio of 0.72.

In Group II (proton centers), patients will be randomized to either conventional photon irradiation with concomitant and adjuvant temozolomide (control arm A2) or dose-escalated and -intensified (consequential to the simultaneous integrated boost) proton beam therapy with concomitant and adjuvant temozolomide (experimental Arm C). It is assumed that median overall survival (starting from randomization) for control arm A2 will be 16 months. It is hypothesized that experimental arm C will lead to median overall survival of 22.2 months, corresponding to a hazard ratio of 0.72.

Within each group, patients will be randomized 1:2 in favor of the experimental arms (B and C). For each group, a total of 141 deaths (combination of control and experimental arms) has 80% power to detect the hypothesized 28% hazard reduction of the experimental therapy in overall survival at the type I error of 0.15 (1-sided); 230 eligible patients in each group are needed. Assuming that 15% of enrolled patients will not be randomized due to insufficient tissue, consent withdrawal, or other reasons and another 5% will be subsequently found ineligible, **the estimated accrual will 288 patients in each group (576 overall)**.

Given the slow accrual to the advanced imaging part of the study (see Section 13.6.6), in December 2016, we amended the protocol to add an additional 30 slots to Group I. These additional slots will only be open to credentialed advanced imaging sites (patient must agree to participate in the advanced imaging sub-study), so that there will be an overall 40 eligible patients enrolled in this part of the study. Given this change, the overall estimated accrual to Group I is increased to 318 patients, whereas the estimated accrual to Group II remains at 288 patients.

13.3.2 Statistical Power for Symptom and Neurocognitive Function Endpoints

The power calculations for both the comparison between arms within each group and that between the experimental arms will be provided for the system and neurocognitive function endpoints. The comparison between the experimental arms will be used to determine what arm(s) will be in the phase III study (see Appendix V).Perceived cognitive function will be measured by the MDASI-BT cognitive factor grouping and neurocognitive function will be measured using a composite score from the Hopkins' Verbal Learning Test-Revised (HVLT-R), Trail Making Test Parts A and B (TMT A, TMT B), and Controlled Oral Word Association Test (COWA). In the recently completed RTOG 0825, early change in the cognitive symptom factor grouping was found to be prognostic for overall survival (HR 1.66; CI 1.20, 2.29; p=0.002) and was sensitive to between arm treatment effect in progression-free patients at discrete time points (p=0.05) and longitudinally over time (Armstrong, Won et al. 2013). Also in RTOG 0825, baseline cognitive function (CTB Composite, HR=1.34; 95% CI=1.08, 1.68; p=0.009) and early change in the cognitive function was found to be prognostic for overall survival (CTB Composite, HR=1.40; 95% CI=1.05, 1.87; p=0.024) and was sensitive to between arm treatment effect in progression-free patients longitudinally over time (p=0.05) (Wefel, Pugh et al. 2013).

Given participation rates in past RTOG trials, it is expected that 85% of patients will consent to participate in this component. It is projected that there will be 196 patients, of the 230 evaluable patients, in each group. Assuming 70% of those participating are compliant at the pre-treatment and 6-month follow-up time points, there will be 136 evaluable patients, 91 on experimental arm and 45 on control arm due to the 2:1 randomization ratio, for each group.

The meaningful effect size for quality of life tools is still in debate. Cohen's widely used rules of thumb for interpreting the magnitude of difference define 0.8 standard deviation (SD) as a "large" effect size, 0.5 SD as a "medium" effect size, and 0.2 SD as a " small" effect size (Cohen 1988). Consensus from the literature seems to indicate that 0.5 SD is a conservative estimate of an effect size that is likely to be clinically meaningful. In the absence of other information, the 0.5 SD is a reasonable and scientifically supportable estimate of a meaningful effect. Effect size below 0.5 SD, supported by data regarding the specific characteristics of a particular quality of life assessment or application, may also be meaningful (Sloan 2005). This discussion is also very applicable to the MDASI-BT and the neurocognitive function tools.

For Group I (IMRT centers), using a 2-sample t-test with a 2-sided alpha=0.1, using a Bonferroni adjustment to account for the neurocognitive function and symptoms assessments resulting in an overall type I error of 0.2, there will be 86% statistical power to detect a medium effect size of 0.5 for a comparison of the change from baseline (prior to step 2 registration) to day 1 of cycle 4 between the experimental arm B and the control arm A1. For Group II (proton centers), a 2-sample t-test will also be used with a 2-sided alpha=0.1, using a Bonferroni adjustment resulting in an overall type I error 0,2, there will be 86% statistical power to detect a medium effect size of 0.5 for a comparison of the change from baseline to day 1 of cycle 4 between the experimental arm C and the control arm A2. For the comparison between experimental arms, there will be 92% power to detect the same effect size using a 2-sample t-test with a 2-sided alpha=0.05.

13.4 Randomization

Patients will be stratified by RPA class (III vs. IV vs. V) and MGMT status (methylated, unmethylated, and indeterminate). This results in 9 strata, and randomization will be conducted within each stratum. Patients will be randomized to either the control arm or experimental arm in each group, with the randomization ratio of 1:2 in favor of experimental arms. The treatment allocation schemes are described by Zelen (1974); permuted block randomization will be used.

13.5 Patient Accrual

It is expected that the monthly accrual will be 8 cases in each group. Thus, the original estimated accrual of 288 cases in each group is expected to be met within 40 months after trial activation, allowing for slow accrual in the first 6 months. If the total accrual during months 13 through 18 after trial activation is ≤ 20% of the targeted accrual (≤ 1.6 cases per month in each group), the protocol will be discontinued. If the total accrual is between 21% and 49%, the protocol will continue to accrue subject to approval of the NRG Data Monitoring Committee (DMC) and NCI. If continued, the study must accrue at least 50% of targeted accrual (> 4 cases per month each group) during months 22 through 24 to remain open beyond 2 years.

With respect to the additional accrual of 30 patients in Group I, based on the up-to-date accrual rate of the credentialed advanced imaging sites on this trial, it is projected that the monthly accrual rate of those sites will be 4 cases. Therefore, the additional accrual is expected to be met within 9 to 10 months after the amendment is approved, considering the time needed for site IRBs to approve the amendment.

13.6 Statistical Analysis Plan (8/7/15)

13.6.1 Time to Event Endpoints

The primary endpoint is overall survival (OS), which will be measured from the date of randomization to the date of death or, otherwise, the last follow-up date on which the patient was reported alive. Progression-free survival (PFS), a secondary endpoint, will be measured from the date of randomization to the date of progression (as reported by the institution), death, or, otherwise, the last follow-up date on which the patient was reported alive. OS and PFS rates will be estimated using the Kaplan-Meier method, and differences between treatment arms will be tested in a stratified log-rank test, consistent with the stratified randomization. The OS rates by MGMT, RPA class and other prognostic factors will be estimated by Kaplan-Meier methods and compared using the log-rank test. Multivariate analyses with the Cox proportional hazard model for OS will be performed to assess the treatment effect adjusting for patient-specific risk factors.

The covariates evaluated for the multivariate models include: assigned protocol treatment, stratification factors (MGMT and RPA class), the interaction of treatment with stratification factors, and other prognostic factors. Proportional hazard assumptions will be checked using different graphical or time-varying coefficients testing methods. If the data clearly do not follow proportional hazards, other statistical models will be used to fit the data instead. Possible alternatives include the stratified Cox proportional hazard model, accelerated failure model, or partitioning the time axis into sections where the proportional hazard assumption holds.

The primary analyses of the primary endpoint are the OS comparisons between the control arm and experimental arm at the overall type I error of 0.15 (1-sided) within each group. If the instrumental variable assumptions (see Section 13.6.3) are met and significant differences between arms are found within both groups, then the overall survival comparisons between the 2 experimental arms will also be performed at the significance level of 0.3 (2-sided), with the recognition that this is a non-definitive comparison due to the lack of direct randomization and the high type 1 error. If the instrumental variable assumptions are not met, there will be no overall survival comparison between the 2 experimental arms.

In order to remove one of the challenges to timely initiation of protocol therapy at proton centers, the protocol was amended to relax the restriction on using MGMT results from LabCorp for stratification and randomization. For patients whose MGMT results from LabCorp are used for stratification, post hoc central MGMT analyses will be performed at MDACC-MDL. Given this change, the concordance on the MGMT results between LabCorp and MDACC-MDL will be evaluated and sensitivity analyses will be performed using the MGMT results from the central analyses at MDACC-MDL for all patients for the above-mentioned endpoints.

13.6.2 Treatment-Related Toxicities

Differences in observed severities of toxicities (grade 3+) between groups will be estimated using an exact binomial distribution together with 95% confidence interval. The difference between the 2 groups will be tested using a chi square test. If the instrumental variable assumptions hold (see Section 13.6.3), the experimental arms will also be compared.

13.6.3 Instrumental Variable Analysis to Compare Experimental Arms

As a secondary objective, this trial seeks to compare treatment efficacy between the experimental dose-escalated and -intensified arms. Randomization between experimental arms is not feasible given the limited availability of proton centers. To enable a comparison of experimental arms to each other, while removing measured and potentially unmeasured confounding, an instrumental variable analysis will be employed.

To conduct an instrumental variable analysis, the following requisite criteria for an instrumental variable must be met (Brookhart, Rassen et al. 2010): 1) an instrumental variable should be closely associated with the likelihood of receiving a treatment; 2) an instrumental variable should be unrelated to patient characteristics; and 3) an instrumental variable should be related to the outcome only through its association with treatment. Therefore, an instrumental variable should have no direct or indirect effect on outcome.

In this trial, group (group I or group II) will be used as the instrumental variable and will satisfy criterion 1, since the proton beam therapy experimental arm will only be available at proton centers and the photon IMRT experimental arm will only be available at photon IMRT centers. To satisfy criteria 2 and 3, the control arms from each group will be compared in terms of baseline patient characteristics and treatment efficacy.

We anticipate that no significant differences (in terms of a 2-sided p value of greater than 0.3) will be apparent in the above comparisons, in which case all criteria for an instrumental variable will be met and a comparison of the experimental dose-escalation/intensification strategies in terms of treatment efficacy and symptom burden will be performed. Six baseline characteristics (age, KPS, gender, baseline neurologic function, MGMT status, and RPA) will each be tested using chi-

square tests for categorical variables and Wilcoxon rank sum test for continuous variables at alpha=0.05 (overall type I error of 0.3, after a Bonferroni correction). Overall survival will be estimated using the Kaplan-Meier method, and differences between experimental arms will be tested in the log-rank test. At the time of initial analysis (141 events within each group), we expect there will be approximately 150 events among the 2 experimental arms. There will be greater than 80% power to detect the hazard ratio of 0.72 in terms of overall survival at the significance of 0.30 (2-sided).

If significant differences are appreciated, then the requisite criteria of an instrumental variable will be violated and a comparison between the experimental dose-escalation/intensification strategies will be abandoned due to concerns of unmeasured confounding.

13.6.4 CD4 Lymphopenia

CD4 lymphopenia count will be collected at baseline and throughout treatment and follow-up. The change from baseline to the completion of radiation will be compared between the control and experimental arms in each group using a t-test. If the instrumental variable assumptions hold, then it will be compared between the experimental arms. A repeated measures analysis, using a mixed effects model, will be used to assess the change of CD4 lymphopenia across time. If the instrumental variable assumptions does not hold, two models will be run; one for each group. If the instrumental variable assumptions hold, then only one model will be of interest: the comparison between the experimental arms. Stratification factors (RPA class and methylation status) and other prognostic factors will be used as covariates in the model. If no significant differences in CD4 lymphopenia exist between arms at baseline, then it will be included as an outcome variable. If significant baseline differences exist, it will be included as a covariate in the model to account for these differences.

According to Grossman et al (2011), CD4 count at 2 months after beginning therapy (dichotomized at 200) was shown to be prognostic of OS. This will be assessed here based on the CD4 count at the completion of chemoradiation which matches best to the 2-month time point in Grossman et al (2011), and using a Cox proportional hazards model, or other statistical model as described in Section 13.6.1, Treatment arm, stratification factors, and other prognostic factors will also be considered.

13.6.5 Symptoms and Neurocognitive Function

The primary hypothesis for symptoms is that perceived cognitive symptom severity, as measured by the M.D. Anderson Symptom Inventory Brain Tumor (MDASI-BT), will be significantly higher for patients treated with conventional photon as compared to dose-escalated and -intensified photon radiation therapy and dose-escalated and -intensified proton beam therapy. As exploratory hypotheses, other MDASI-BT factor groupings will be of interest:

1) Treatment-specific symptoms, pruritus, fatigue and nausea, will be significantly higher for patients treated with hypofractionated dose escalation photon radiation therapy then those receiving proton radiation therapy.
2) Mean neurologic (weakness, numbness, and seizures) and interference factor scores will be significantly lower in the proton arm during the course of treatment.
3) Mean neurologic factor item and cognitive factor item (problems remembering, concentrating, and speaking) scores and the mean symptom interference score (based on the symptom interference scale on the MDASI-BT) will correlate with improvement in overall survival.
4) Baseline neurologic function and early change in cognitive function factor score on the MDASI-BT, will be prognostic for overall survival.

The primary hypothesis for neurocognitive function is objectively measured cognitive function, as measured by the Clinical Trial Battery (CTB - consisting of HVLT-R, TMT A and B, COWA) composite score will be significantly worse for patients treated with hypofractionated dose escalation photon radiation therapy compared to those receiving proton radiation therapy.

Additionally of interest is cognition, as measured separately by the HVLT-R, TMT, and COWA test.

In order to examine hypotheses related to the comparison of the experimental arms B and C, the instrumental variable assumptions will need to hold for symptoms and neurocognitive function in addition to the primary endpoint of the study. Therefore, before experimental arm comparisons take place, a comparison between the control arms with respect to the perceived cognitive symptom severity and neurocognitive function composite score will be conducted, each using a 2-sample t-test with alpha = 0.10. If there are no significant differences between the control arms, then the perceived cognitive symptom severity and neurocognitive function composite score will be compared between experimental arms B and C.

The change from baseline (prior to step 2 registration) to each follow-up time point (within 7 days prior to cycle 4 and cycle 12, approximately 24 and 60 weeks, respectively, from chemoRT) for the perceived cognitive symptom severity and CTB composite score will each be compared using a t-test with alpha=0.05, or Wilcoxon test if the data is not normally distributed, between treatment arms within each group. If there is a significant difference in perceived cognitive function, a comparison between arms within each group for the remaining factor groupings and treatment-specific symptoms mentioned in the above hypotheses for MDASI-BT will be conducted. If there is a significant difference in the CTB composite score, then the neurocognitive tests making up the CTB will be tested. If the instrumental variable assumptions hold and the perceived cognitive function and/or CTB composite score is significantly different within both groups, a test will be performed to compare between the 2 experimental arms. If significant, the remaining factor groupings and treatment-specific symptoms mentioned in the hypotheses above for MDASI-BT and/or the CTB neurocognitive tests that were found to be significantly different between arms in both groups will be tested between the experimental arms. Progression and resulting salvage treatment could affect symptom and neurocognitive function results. Therefore, the primary and exploratory hypotheses for symptoms and neurocognitive functioning may be conducted in progression-free patients only or a general linear model may be used to account for progression status at each follow-up time point.

A change in symptom severity of 1 point will be classified as the minimum important difference (MID) for MDASI-BT. The reliable change index (RCI) criteria will be used for the MID for the CTB neurocognitive tests (Jacobsen 1991; Chelune 1993). The deterioration status at 24 and 60 weeks after chemoradiotherapy, with deterioration defined as change from baseline > MID, will be compared between treatment arms within each group (i.e., control vs. experimental). If the instrumental variable assumptions hold, only those factor groupings, treatment-specific toxicities, and neurocognitive tests found to be significantly different between arms in both groups will be compared between the 2 experimental arms.

The prognostic impact of these factor groupings, treatment-specific toxicities, and neurocognitive tests on OS and PFS will be assessed using the multivariate Cox proportional hazards models after accounting for protocol treatment and stratification factors. If the proportional hazards assumption does not hold, alternative methods will be used. Longitudinal models, specifically mixed effects models, will be built using data from baseline and all follow-up time points, while adjusting for progression status, stratification factors, and other covariates of interest. If the instrumental variable assumptions hold, group (group 1 vs. group II), age, KPS, gender, baseline neurologic function, MGMT status, and RPA will also be included as covariates in the model. Only those factors and symptoms mentioned in the above hypotheses will be considered in the longitudinal and prognostic modeling for the MDASI-BT.

Completion of all scheduled assessments is part of the routine delinquency assessment for participating institutions. The Statistics and Data Management Center staff will monitor proportions of missing data in each treatment arm at different assessment points. In spite of these efforts, missing data is to a certain extent expected. The information from patients with missing data will be reviewed to determine whether the data analyses will be biased. Patients with

missing data will be reviewed for the distributions of treatment arms and patient characteristics. Mean scores by assessment time for cohorts stratified by baseline score quartile will also be compared to investigate if the missingness is consistent with an ignorable missing data process (missing at random). If no missing data mechanism can be detected, the data will be analyzed assuming missing data is at random and, if appropriate, imputation for missing values will be conducted. Longitudinal mixed effects models using maximum likelihood estimation can adjust for data that is missing at random as well. If the missing data mechanism appears to be present, we will use appropriate analytic strategies to control for the potential bias and, if possible, to impute the missing data using multiple imputation. The data can also be analyzed using pattern mixture models to estimate separate estimates for the outcome within strata based on the missing data pattern, and then combining estimates in a specialized way to yield appropriate an overall effect estimate (Little and Rubin 2002). Sensitivity analyses based on the varying assumptions about the missing data mechanisms will also be conducted especially if imputing.

13.6.6 Advanced Imaging

Advanced MRI scans will be obtained prior to initiation of radiation treatment and at subsequent follow-up time-points at designated, pre-approved sites on subjects consented and enrolled into the advanced imaging component (See Appendix VIII). The post-operative MRI scan can also be used as the baseline MRI scan as long as advanced imaging protocol guidelines are followed.

Patients enrolled in the optional advanced MR imaging study will undergo DSC and DWI imaging at four time points corresponding to prior to initiation of radiation treatment, Week 3 during chemoradiation (mid-course through treatment), prior to Cycle 1 and prior to cycle 4. Section 1.8 describes the background significance of DSC-MRI and DWI in evaluating treatment response. We hypothesize that early changes in rCBV and ADC will be an important predictor for distinguishing true progression from pseudoprogression. Additional analyses will assess MRI imaging covariates as predictors of response and overall survival.

Quantitative imaging analysis methods are highly sensitive to analyze early treatment-induced changes in tumor cellularity as well as hemodynamic alterations within the tumor. By focusing on regions of increasing or decreasing ADC and rCBV, the functional behavior of the tumor can be spatially analyzed and interpreted for possible prognostic value. (Galban et al, 2009) Additionally histogram analyses will also be performed to determine which method provides the best sensitivity, specificity, and predictive values.

The measure of interest will be early changes in ADC and rCBV values from baseline to specific time-points during the study. (i.e Week 3 during radiation and prior to cycle 1) An optimal threshold value will be confirmed in order to achieve the desired high levels of specificity and sensitivity in determining true progression from pseudoprogression. Pseudoprogression will be determined retrospectively following central review by an experienced neuroradiologist blinded to the patient's outcome. (Brandsma, 2008 Lancet Oncology)

Previously published single institution data demonstrated that significant reductions in fractional tumor volumes of low cerebral blood volume during treatment were noted in patients with progression compared to patients with pseudoprogression. (Tsien et al, 2010) Using a pre-specified threshold, the estimated sensitivity and specificity in predicting progression was 94% and 80% respectively. Sensitivity and specificity will be estimated with associated 95% CIs.

The primary outcome measure will be response rate at 10 weeks post-radiation treatment (prior to Cycle 1). The change in the imaging parameters between baseline and week 3 during radiation is of primary interest, as the predictor of the model. However, changes between baseline and other time points will also be considered. Known prognostic factors and patient baseline characteristics will be included in the multivariate analyses as covariates.

Response rate at 3 months post-radiation treatment (prior to Cycle 4) as well as overall survival at 12 months will be analyzed as the outcome variable in separate logistic regression models, and

predictors will be changes in the MR imaging parameters between baseline and specific early time points in the study. Known prognostic factors and patient baseline characteristics will be included in the regression models. Leave-one-out cross validation will be employed for predictive assessment of the imaging parameters. The change between baseline and Week 3 during radiation is of primary interest. However, other time points including changes between baseline and prior to cycle 1 will also be considered.

Thresholds at which to dichotomize will be obtained from prior published results. (Galban, 2009) Specifically, fractional tumor volume that has an increase in PRM_{ADC} greater than 4.7% was found to be associated with increased overall survival. Stepwise regression methods will be used for variable selection in all statistical models. The c-statistic will be used to assess model fit and cross-validation will be employed.

Time-dependent ROC analysis will be used to assess the ability of each marker to predict response rate at 3 months post radiation and overall survival rate at 12 months. In this analysis, ROC curves for each marker will be estimated for each time point. The estimated ROC curves will be used to determine threshold values for the optimal prediction of tumor response and overall survival at the specified time-points. In particular, the threshold value for each marker will be chosen to provide the optimal combination of sensitivity and specificity on the ROC curve (corresponding to the point on the ROC curve that is closest to the point where sensitivity=1 and specificity=1). Comparison of the markers will be made using the area under the respective ROC curves.

Power/Sample Size Justification
Sample size determination is based on preliminary, single institution, data of 45 subjects evaluated with PRM_{ADC} and 41 subjects evaluated with PRM_{rCBV}.

The primary analysis will be focused on PRM_{ADC}. For sample size and power considerations, we will assume that the estimated true positive rate is 0.85 and true negative rate is 0.60, respectively, where we define true positive rate as the probability that a subject is responsive at week 10 given that he/she was responsive at week 3, and true negative rate as the probability that, given that a patient is non-responder at week 3, he/she is also non-responsive at week 10. In this analysis, the estimated true positive rate is defined as a responder based on early advanced MR imaging biomarkers obtained at Wk3 during RT and subsequently confirmed as a radiographic responder at Wk.10 post chemo-radiation. (Hamstra D A, Galban CJ, Meyer CR, et al. Functional diffusion map as an early imaging biomarker for high-grade glioma: correlation with conventional radiologic response and overall survival. J Clin Oncol. 2008;26(20):3387-3394)

We will consider three different scenarios. First, for scenario 1, we assume no over dispersion due to clinic differences and assume binomial models for the true positive and true negative counts with probabilities 0.85 and 0.60, respectively for the true positive and true negative rates. For the other two scenarios, we will assume over dispersion and use beta-binomial models for the true positive and true negative counts. We simulate data by drawing the true positive and true negative rates from a beta distribution with parameters $\alpha = 80, \beta = 20$ for the true positive rate and $\alpha = 65, \beta = 35$ for the true negative rate for scenario 2, and $\alpha = 40, \beta = 10$ and $\alpha = 37.5, \beta = 17.5$, respectively for scenario 3. For each scenario, we draw the number of responders at 3 weeks from a binomial distribution with a parameter of 0.5. Given the number of responders and non-responders at 3 weeks, we then sampled the number of correctly classified patients based on either scenario 1, 2 or 3.

10000 simulations were performed for each scenario assuming a sample size of 40 subjects and computed power by determining the number of simulations that resulted in a statistically significant PRM parameter at a nominal significance level of 0.05 using a one-sided test (the primary interest is in PRM measures having a better than equal chance of predicting the truth).

The primary endpoint is response rate at 10 weeks post chemo-RT. We use Fisher exact test to determine whether the response rate at 10 weeks based on conventional MRI is associated with the response as determined using advanced MR imaging parameters obtained at baseline and Wk3 during treatment. An analogous simulation study was performed for PRM_{rCBV}. For power considerations, we then estimated true positive rate is 0.75 and estimated true negative rate is 0.60, respectively. Three simulation scenarios are considered: No over dispersion and 2 levels of over dispersion. For scenario 2, we assume over dispersion from the binomial model by drawing true positive rates from a beta distribution with parameters $\alpha = 75, \beta = 25$ and true negative rates from a beta distribution with parameters $\alpha = 60, \beta = 40$. For scenario three, we use more over dispersion and draw rates from beta distributions with parameters $\alpha = 37.5, \beta = 12.5$ and $\alpha = 30, \beta = 20$, respectively for true positive and negative rates. The following tables summarize power for a sample size of 40 subjects when the proportion of responders at 3 weeks is 50%. .

Proportion of responders at 3 weeks	Simulation scenario	PRM_{ADC}	PRM_{rCBV}
50%	Scenario 1	0.91* (0.85**)	0.75*
50%	Scenario 2	0.90* (0.83**)	0.74*
50%	Scenario 3	0.88* (0.81**)	0.73*

*: using a significance level (alpha) of 0.1
**: using a significance level (alpha) of 0.05

By December 2016 (before the sample size increase), there have been 17 eligible patients enrolled in the advanced imaging part of the study. We amended the protocol to add an additional 30 slots limited to the credentialed advanced imaging sites. Therefore, there will be an overall of at least 40 eligible patients enrolled in this part of the study, given that a small percentage of the patients accrued may be ineligible.

13.7 Interim and Final Analysis (8/7/15)

13.7.1 Special Interim Toxicity Analysis

Due to a possible increased incidence of grade 3+ CNS toxicity (possibly, probably, or definitely related to treatment) occurring during the first 6 months post-radiation in the experimental arm, two special interim analyses will be performed after the first 20 and 38 patients enrolled to the experimental arm have a minimum 6-month follow-up. If the incidence of grade 3+ CNS toxicity for 20 patients (5% based on RTOG 0525) is higher by an absolute increase of 15% to a total incidence of 20% in either experimental arm, the trial will be halted due to lack of safety. Assuming the study remains open, another interim analysis will be conducted once 38 patients have 6 months follow-up. If at least 5 of 38 patients (13%) experience grade 3+ CNS toxicity, the study will be halted due to lack of safety. The interim toxicity analysis results will be reported to the NRG DMC. The DMC will then make a recommendation about the trial to the NRG Group Co-Chairs.

13.7.2 Interim Analysis for Early Termination and Reporting

Interim treatment comparisons for each group will be performed when we observe 50% (71 deaths) of the 141 required maximum number of deaths per group. The analysis will be done on an intent-to-treat basis, with all eligible cases being included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. The primary endpoint of overall survival will be tested at the interim analysis. If the observed hazard ratio (experimental/control) is greater than or equal to 1.0, then the corresponding cohort will be terminated early at the interim analysis for futility (i.e., the experimental arm will be considered ineffective in this disease population) and the results will be reported. If the observed hazard ratio of the experimental arm relative to the standard arm is less than 1.0, then the trial will continue to

the full target accrual. Under reasonable assumptions, termination of the corresponding cohort for futility at the interim analysis using this rule is found to result in minimal loss of power (less than 2%) for the primary hypothesis test (Wieand, Schroeder et al. 1994). If the observed hazard ratio (experimental/standard) is ≥ 1.0, a decision about whether to terminate accrual to the group and release group-specific results will be made. The accrual rate, treatment compliance, safety of the treatments, and the importance of the study are also considered in making such a decision. The results will be reported to the NRG DMC with the treatment blinded. The DMC will then make a recommendation about the trial to the NRG Group Co-Chair.

13.7.3 Significance Testing for Final Analysis

The final analysis will be done on an intent-to-treat basis, such that all eligible cases on the study will be included in the arm to which they were randomized regardless of what treatment the patients actually received. The analysis to report the final results of treatment comparison between the experimental arms and the control arm will be undertaken when 141 events (deaths) have been reported per group. A 1-sided log-rank test will be performed to test the difference in overall survival between the experimental arm and control arm within each group. If the p value is less than protocol-specified 0.15 (1-sided), the study statistician will reject the null hypothesis and conclude that the experimental arm is promising in prolonging overall survival, therefore supporting the development of a confirmatory phase III trial comparing this regimen to the current standard treatment. All information reported in the interim analyses to monitor the study progress (above) will also be included in the final report.

If the criteria for the group (group I vs. group II) as an instrumental variable are met, the comparison of overall survival between the 2 experimental arms will be performed (as described in 6.4.3) through a 2-sided log-rank test. If the p value is less than 0.3, the study statistician will reject the null hypothesis and conclude that the 2 experimental arms may not be same in terms of overall survival, therefore supporting the development of a confirmatory phase III trial comparing the proton experimental arm to the standard control arm.

Continuation to a phase III trial will be determined using the rules outlined in Appendix V.

13.7.4 Interim Analysis To Monitor Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase; rates of patient exclusion rates due to ineligibility and failure to be randomized following registration; compliance rate of treatment delivery; the frequencies and severity of treatment-related adverse events by treatment arm; and the assay performance with regard to turn-around time (defined as the time between the dates of tissue collection and randomization) and failure rate (defined as the percentage of assays that fall in the undetermined category). The interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints (overall survival, treatment response). The NRG DMC will review the accrual to the study and the rate of adverse events on the study at least twice per year until the initial results of the study have been presented to the scientific community.

13.7.5 CDUS Reporting

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

13.8 Gender and Minorities

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	10	18	28
Not Hispanic or Latino	251	327	578
Ethnic Category: Total of all subjects	261	345	**606**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	1	1	2
Asian	6	4	10
Black or African American	5	8	13
Native Hawaiian or other Pacific Islander	1	1	2
White	248	331	579
Racial Category: Total of all subjects	261	345	**606**

REFERENCES (10/6/14)

Armstrong TS, Mendoza T, Gning, C, et al. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). J Neurooncol. 2006;80(1):27-35.

Armstrong TS, Vera-Bolanos E, Gning E, et al. The impact of symptom interference using the MD Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT) on prediction of recurrence in primary brain tumor patients. Cancer. 2011;117(14):3222-3228.

Armstrong TS, Wefel JS, Wang M, et al. Net Clinical Benefit Analysis of Radiation Therapy Oncology Group 0525: A phase III trial comparing conventional adjuvant temozolomide with dose-Intensive temozolomide in patients with newly diagnosed glioblastoma. J Clin Oncol. 2013;31(32):4076-84.

Bleehen NM, Stenning SP. A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. The Medical Research Council Brain Tumour Working Party. Br J Cancer. 1991;64(4):769-774.

Brookhart MA, Rassen JA, Schneeweiss S. Instrumental variable methods in comparative safety and effectiveness research. Pharmacoepidemiol Drug Saf. 2010;19(6):537-554.

Cao Y, Tsien CI, Nagesh V, et al. Survival prediction in high-grade gliomas by MRI perfusion before and during early stage of RT [corrected]. Int J Radiat Oncol Biol Phys. 2006;64(3):876-885.

Cao Y, Sundgren PC, Tsien CI, et al. Physiologic and metabolic magnetic resonance imaging in gliomas. J Clin Oncol. 2006;24(8):1228-35.

Cao Y, Shen Z, Chenevert TL, Ewing JR. (2006). Estimate of vascular permeability and cerebral blood volume using Gd-DTPA contrast enhancement and dynamic T2*-weighted MRI. J Magn Reson Imaging. 2006;24(2):288-296.

Chan JL, Lee SW, Fraass BA, et al. Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy." J Clinical Oncol. 2002;20(6):1635-1642.

Chelune GJ, Naugle RI, Luders H, et al. Individual change after epilepsy surgery: practice effects and base-rate information. Neuropsychology. 1993;7:41-52

Chenevert TL, Stegman LD, Taylor JM, et al. Diffusion magnetic resonance imaging: an early surrogate marker of therapeutic efficacy in brain tumors. J Natl Cancer Inst. 2000;92:2029-36.

Chu HH, Choi SH, Ryoo I, et al. Differentiation of true progression from pseudoprogression in glioblastoma treated with radiation therapy and concomitant temozolomide: comparison study of standard and high-b-value diffusion-weighted imaging. Radiology. 2013;Jun 14, epub.

Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer. 2000;89(7):1634-1646.

Cleeland CS, Sloan JA. Assessing the Symptoms of Cancer Using Patient-Reported Outcomes (ASCPRO): searching for standards. J Pain Symptom Manage. 2010;39(6):1077-1085.

Colman H, L. Zhang L, Sulman EP, et al. A multigene predictor of outcome in glioblastoma. Neuro Oncol. 2010;2(1):49-57.

Cohen J. Statistical power analysis for the behavioral sciences. Lawrence Erlbaum Associates, Hillsdale, New Jersey, 1988.

Curran WJ Jr, Scott CB, Horton J, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials." J Natl Cancer Inst. 1993;85(9):704-710.

Esteller M, Garcia-Foncillas JE, Andion SN, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. N Engl J Med. 2000;343(19):1350-1354.

Fitzek MM, Thornton AF, Rabinov JD, et al. Accelerated fractionated proton/photon irradiation to 90 cobalt gray equivalent for glioblastoma multiforme: results of a phase II prospective trial. J Neurosurgery. 1999;91(2):251-260.

Galban CJ, Chenevert TL, Meyer CR, et al. The parametric response map is an imaging biomarker for early cancer treatment outcome. Nat Med. 2009;15(5):572-576.

Galban CJ, Chenevert TL, Meyer CR, et al. Prospective analysis of parametric response map-derived MRI biomarkers: identification of early and distinct glioma response patterns not predicted by standard radiographic assessment. Clin Cancer Res. 2011;17(14):4751-4760.

Gilbert MR, Wang M, Aldape KD, et al. RTOG 0525: A randomized phase III trial comparing standard adjuvant temozolomide with a dose-dense schedule in newly diagnosed glioblastoma. J Clin Oncol. 2011;29:abstr 2006.

Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):699-708.

Grossman SA, Ye X, Lesser G, et al. Immunosuppression in patients with high-grade gliomas treated with radiation and temozolomide. Clin Cancer Research. 2011;17(16):5473-5480.

Grossman SA, Ye X, Piantadosi S, et al. Survival of patients with newly diagnosed glioblastoma treated with radiation and temozolomide in research studies in the United States. Clin Cancer Res. 2010;16(8):2443-2449.

Hamstra D A, Galban CJ, Meyer CR, et al. Functional diffusion map as an early imaging biomarker for high-grade glioma: correlation with conventional radiologic response and overall survival. J Clin Oncol. 2008;26(20):3387-3394.

Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352(10):997-1003.

Hughes MA, Parisi M, Grossman S, Kleinberg L. Primary brain tumors treated with steroids and radiotherapy: low CD4 counts and risk of infection. Int J Radiat Oncol Biol Phys. 2005;62(5):1423-1426.

ICRU 78: Prescribing, recording and reporting proton-beam therapy. J ICRU. 2007;7(2):NP.

Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991;59:12-19

Johnson DR, Sawyer AM, Meyers CA, et al. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. Neuro Oncol. 2012;14(6):808-16, 6/2012. e-Pub 4/2012.

Kahalley LS, Fatih Okcu M, Douglas Ris M, et al. IQ change within three years of radiation therapy in pediatric brain tumor patients treated with proton beam versus photon radiation therapy. J Clin Oncol. 2013;31(suppl; abstr 10009)

Komar G, Seppanen M, Eskola O et al. 18F-EF5: a new PET tracer for imaging hypoxia in head and neck cancer. J Nucl Med. 2008;49(12):1944-1951.

Le QT, Courter D.Clinical biomarkers for hypoxia targeting. Cancer Metastasis Rev. 2008;27(3):351-362.

Li J, Wang M, Won M, et al. Validation and simplification of the Radiation Therapy Oncology Group recursive partitioning analysis classification for glioblastoma. Int J Radiat Oncol Biol Phys. 2011;81:623-630.

Liu W, Zhang X, Li Y, Mohan R. Robust optimization of intensity modulated proton therapy. Med Phys. 2012;39(2):1079-1091.

Lord EM, Harwell L, Koch CJ. Detection of hypoxic cells by monoclonal antibody recognizing 2-nitroimidazole adducts. Cancer Res. 1993;53(23):5721-5726.

Macdonald D, Cascino T, Schold SJ, et al. Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol. 1990;8:1277-1280.

Merchant TE, Pollack IF, Loeffler JS. Brain tumors across the age spectrum: biology, therapy, and late effects. Semin Radiat Oncol. 2010;20(1):58-66.

Merchant TE, Hua CH, Shukla H, et al. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatr Blood Cancer. 2008;51(1):110-7.

Milano MT, Okunieff P, Donatello RS, et al.Patterns and timing of recurrence after temozolomide-based chemoradiation for glioblastoma. Int J Radiat Oncol Biol Phys. 2010;78(4):1147-1155.

Mizoe JE, Tsujii H, Hasegawa A, et al. Phase I/II clinical trial of carbon ion radiotherapy for malignant gliomas: combined X-ray radiotherapy, chemotherapy, and carbon ion radiotherapy. Int J Radiat Oncol Biol Phys. 2007;69(2):390-396.

Mizumoto M, Tsuboi K, Igaki H, T, et al. Phase I/II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2010;77(1):98-105.

Moffat BA, Chenevert TL, Lawrence TS, et al. Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response. Proc Natl Acad Sci U S A. 2005;102(15):5524-5529.

Nakagawa K, Aoki Y, Fujimaki T, et al. High-dose conformal radiotherapy influenced the pattern of failure but did not improve survival in glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 1998;40(5):1141-1149.

Nordsmark M, Overgaard J. A confirmatory prognostic study on oxygenation status and loco-regional control in advanced head and neck squamous cell carcinoma treated by radiation therapy. Radiother Oncology. 2000;57(1):39-43.

Noushmehr H, Weisenberger DJ, Diefes K, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell. 2010;17(5):510-522.

Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol. 2012;57(11):R99-R117.

Park HC, Janjan NA, Mendoza TR, et al. Temporal patterns of fatigue predict pathologic response in patients treated with preoperative chemoradiation therapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2009;75(3):775-781.

Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321(5897):1807-1812.

Pope WB, Hessel C. Response assessment in neuro-oncology criteria: implementation challenges in multicenter neuro-oncology trials. AJNR Am J Neuroradiol. 2011;32(5):794-797.

Ray-Coquard I, Cropet C, Van Glabbeke M, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas and lymphomas. Cancer Res. 2009;69(13):5383-5391.

Reddy K, Damek D, Gaspar LE, et al. Phase II trial of hypofractionated IMRT with temozolomide for patients with newly diagnosed glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2012;84(3):655-660.

Rosenthal DI., Mendoza TR, Chambers MS, et al.The M. D. Anderson symptom inventory-head and neck module, a patient-reported outcome instrument, accurately predicts the severity of radiation-induced mucositis. Int J Radiat Oncol Biol Phys. 2008;72(5):1355-1361.

Sabin ND, Merchant TE, J. H. Harreld JH, et al. Imaging changes in very young children with brain tumors Treated with proton therapy and chemotherapy. AJNR Am J Neuroradiol. 2012;34(2):446-50.

Said HM, C. Hagemann C, A. Staab A, et al. Expression patterns of the hypoxia-related genes osteopontin, CA9, erythropoietin, VEGF and HIF-1alpha in human glioma in vitro and in vivo. Radiother Oncol. 2007;83(3):398-405.

Sathornsumetee S, Cao Y, Marcello JE, et al. Tumor angiogenic and hypoxic profiles predict radiographic response and survival in malignant astrocytoma patients treated with bevacizumab and irinotecan. J Clin Oncol. 2008;26(2):271-278.

Schoenfeld DA. Sample-size formula for the proportional-hazards regression model, Biometrics. 1983;39(2):499-503.

Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncology. 2009;10(5):459-466.

Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma." N Engl J Med. 2005;352(10):987-996.

Su YB, Sohn S, Krown SE, et al. Selective CD4 lymphopenia in melanoma patients treated with temozolomide: a toxicity with therapeutic implications. J Clin Oncol.2004;22(4):610-16.

Sulman EP, Cahill DP, Wang M, et al. A combined molecular clinical predictor of survival validated with the RTOG-0525 cohort. Abstract OM-30. Neuro Oncol. 2011. 13, iii76-iii84.

Tanaka M, Ino Y, Nakagawa K, et al. High-dose conformal radiotherapy for supratentorial malignant glioma: a historical comparison. Lancet Oncology. 2005;6(12):953-960.

Tsien C, Galban CJ, Chenevert TL, et al. Parametric response map as an imaging biomarker to distinguish progression from pseudoprogression in high-grade glioma. J Clin Oncol. 2010;28(13):2293-2299.

Tsien CI Brown D, Normolle D, et al. Concurrent temozolomide and dose-escalated intensity-modulated radiation therapy in newly diagnosed glioblastoma. Clin Cancer Res . 2012;18(1):273-279.

Walker MD, Strike TA, Sheline GE. An analysis of dose-effect relationship in the radiotherapy of malignant gliomas. Int J Radiation Oncol Biol Phys. 1979;5(10):1725-1731.

Wang X.S, Shi Q, C. Lu C, et al. Prognostic value of symptom burden for overall survival in patients receiving chemotherapy for advanced nonsmall cell lung cancer. Cancer. 2010;116(1):137-145.

Wefel JS, Pugh S, Armstrong TS, et al. Longitudinal analysis of neurocognitive outcomes in patients with glioblastoma (GBM) enrolled in RTOG 0825. Oral presentation at the 4th Quadrennial Meeting of the World Federation of Neuro-Oncology held in conjunction with the Scientific Meeting and Education Day of the Society for Neuro-Oncology, San Francisco, CA, November 21, 2013

Wen, PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010;28(11):1963-1972.

Zelen M. The randomization and stratification of patients to clinical trials. J Chron Dis. 1974;27:365-375.

APPENDIX I (2/16/17)

STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENT

	Prior to Step 1 Registration	Prior to Step 2 Registration	
Assessments		≤14 d	≤28 d
Central tissue evaluation for histology & sample adequacy		As soon as possible after surgery (see Section 10.2)	
Contrast-enhanced MRI	≤72 hours after surgery If MRI not obtained ≤72 hours after surgery, then MRI obtained ≥2 weeks after surgery is required		
Serum pregnancy test (females of child-bearing potential			X
History/Physical/ Performance Status			X
Documentation of steroid dose			X
CBC w/ diff, ANC, platelets, Hgb			X
Bilirubin			X
ALT/AST			X
CD4 count			Recommended prior **to treatment start**
EKG			If clinical suspicion of cardiac issue
Advanced MRI Imaging (for consented patients enrolling on the advanced imaging component at advanced imaging-qualified institutions. See Appendix VIII for further imaging guidelines)			≤28 d prior **to treatment start**
Informed consent	X		
Tissue for banking (for consenting patients)		X	
Blood for banking (for consenting patients)			≤28 d prior **to treatment start**
Urine for banking (for consenting patients)			≤28 d prior **to treatment start**
Patient-Reported Outcomes MDASI-BT			X
Neurocognitive Function HVLT-R TMT A/B COWA			X

APPENDIX I (continued)

STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT

	During Chemo-RT		Adjuvant Phase (i.e., up to12 cycles of temozolomide. Patients who discontinued treatment after 6 cycles should still have the same assessments as described for patients continuing treatment up to 12 cycles)			
Assessments	Wkly	q2wks	Within **72 hours** prior to d1 of cycle 1	Within **7 days** prior to d1 of cycles 1, 4, 7 and 10	d28 (± 3d) of each cycle, prior to starting the next cycle (including cycle 12)	d22-d28 of cycle 12
History/Physical/ Performance Status			X		X	
Adverse event eval	X		X		X	
Steroid dose documentation			X		X	
CBC w/ diff, ANC, platelets, Hgb		X	X		X And at day 21 (±48h) of each cycle	
Bilirubin		X	X		X	
ALT/AST		X	X		X	
CD4 count (as recommended per Section 11.2)		Strongly recommended at 4 weeks during chemo-RT and at completion of chemo-RT	Strongly recommended		Strongly recommended	
Patient-Reported Outcomes ☐ MDASI-BT				1 time point: Within 7d prior to d1 of cycle 4**		X**
Neurocognitive Function ☐ HVLT-R ☐ TMT A/B ☐ COWA				1 time point: Within 7d prior to d1 of cycle 4**		X**

**Patent-reported outcomes and neurocognitive function assessments should be performed as close to the day of the contrast-enhanced MRI as possible. Assessments must be completed regardless of progression or discontinuation of treatment.

Continued on next page

APPENDIX I (continued)

STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT

	During Chemo-RT		Adjuvant Phase (i.e., up to12 cycles of temozolomide. Patients who discontinued treatment after 6 cycles should still have the same assessments as described for patients continuing treatment up to 12 cycles)			
Assessments	Wkly	q2wks	Within **72 hours** prior to d1 of cycle 1	Within **7 days** prior to d1 of cycles 1, 4, 7 and 10	d28 (± 3d) of each cycle, prior to starting the next cycle (including cycle 12)	d22-d28 of cycle 12
Contrast-enhanced MRI				X		X
Tumor response eval per Macdonald criteria				X		X
Advanced MR Imaging (for consented patients enrolling on the advanced imaging component at advanced imaging-qualified institutions. See Appendix VIII for further imaging guidelines)*	Wk. 3 (+/-1 wk) during chemo-RT			2 time points: Within 7d prior to d1 of cycles 1 and 4		

*Advanced imaging must be completed regardless of progression or discontinuation of treatment.

APPENDIX I (continued)
STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW-UP

Assessments	Following completion of adjuvant phase (ie, d28 of C12), q 3 mos for 1 year, then q 4 mos for year 2, then q 6 mos thereafter
History/Physical/ Performance Status	X
Steroid dose documentation	X
Adverse event eval	X
Contrast-enhanced MRI	X
Tumor response eval per Macdonald criteria	X

APPENDIX II

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

KARNOFSKY PERFORMANCE SCALE

100	**Normal; no complaints; no evidence of disease**
90	**Able to carry on normal activity; minor signs or symptoms of disease**
80	**Normal activity with effort; some sign or symptoms of disease**
70	**Cares for self; unable to carry on normal activity or do active work**
60	**Requires occasional assistance, but is able to care for most personal needs**
50	**Requires considerable assistance and frequent medical care**
40	**Disabled; requires special care and assistance**
30	**Severely disabled; hospitalization is indicated, although death not imminent**
20	**Very sick; hospitalization necessary; active support treatment is necessary**
10	**Moribund; fatal processes progressing rapidly**
0	**Dead**

APPENDIX III

NEUROLOGIC FUNCTION STATUS

0	**No neurologic symptoms; fully active at home/work without assistance**
1	**Minor neurologic symptoms; fully active at home/work without assistance**
2	**Moderate neurologic symptoms; fully active at home/work but requires assistance**
3	**Moderate neurologic symptoms; less than fully active at home/work and requires assistance**
4	**Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution--unable to work**

APPENDIX IV (10/6/14)

Recursive Partitioning Analysis (RPA) System

Class III	Age < 50 and KPS 90-100
Class IV	Age < 50 and KPS < 90; **OR** age ≥ 50 and KPS 70-100 and partially or total resected with no worse than minor neurofunction impairment
Class V	Age ≥ 50 and KPS 70-100 and underwent prior partial or total tumor resection with worse than minor neurofunction impairment

APPENDIX V
Rules for Continuation to a Phase III Trial

Phase IIR Results	**Level of Significance**	**Anticipated Phase III Trial**
$MS_{IMRT75Gy}$ exceeds MS_{60Gy} $MS_{Proton75Gy}$ does not exceed MS_{60Gy}	p<0.15 (1-sided) p≥0.15 (1-sided)	IMRT 75 Gy versus 60 Gy
$MS_{IMRT75Gy}$ does not exceed MS_{60Gy} $MS_{Proton75Gy}$ exceeds MS_{60Gy}	p≥0.15 (1-sided) p<0.15 (1-sided)	Proton 75 Gy versus 60 Gy
$MS_{IMRT75Gy}$ does not exceed MS_{60Gy} $MS_{Proton75Gy}$ does not exceed MS_{60Gy}	p≥0.15 (1-sided) p≥0.15 (1-sided)	No phase III trial
$MS_{IMRT75Gy}$ exceeds MS_{60Gy} $MS_{Proton75Gy}$ exceeds MS_{60Gy} Instrumental variable assumptions are met. $MS_{IMRT75Gy}$ exceeds $MS_{Proton75Gy}$	p<0.15 (1-sided) p<0.15 (1-sided) p<0.3 (2-sided)	IMRT 75 Gy versus 60 Gy
$MS_{IMRT75Gy}$ exceeds MS_{60Gy} $MS_{Proton75Gy}$ exceeds MS_{60Gy} Instrumental variable assumptions are met. $MS_{Proton75Gy}$ exceeds $MS_{IMRT75Gy}$	p<0.15 (1-sided) p<0.15 (1-sided) p<0.3 (2-sided)	Proton 75 Gy versus 60 Gy
$MS_{IMRT75Gy}$ exceeds MS_{60Gy} $MS_{Proton75Gy}$ exceeds MS_{60Gy} Instrumental variable assumptions are met. $MS_{Proton75Gy}$ no different to $MS_{IMRT75Gy}$ $NCF_{IMRT75Gy}$ superior to $NCF_{Proton75Gy}$ (Irrespective of PRO comparison of IMRT75Gy to Proton 75Gy)	p<0.15 (1-sided) p<0.15 (1-sided) p≥0.3 (2-sided) p<0.05 (2-sided)	IMRT 75 Gy versus 60 Gy

Phase IIR Results	**Level of Significance**	**Anticipated Phase III Trial**
$MS_{IMRT75Gy}$ exceeds MS_{60Gy} $MS_{Proton75Gy}$ exceeds MS_{60Gy} Instrumental variable assumptions are met. $MS_{Proton75Gy}$ no different to $MS_{IMRT75Gy}$ $PRO_{IMRT75Gy}$ superior to $PRO_{Proton75Gy}$ (Irrespective of NCF comparison of IMRT75Gy to Proton 75Gy)	p<0.15 (1-sided) p<0.15 (1-sided) p≥0.3 (2-sided) p<0.05 (2-sided)	IMRT 75 Gy versus 60 Gy
$MS_{IMRT75Gy}$ exceeds MS_{60Gy} $MS_{Proton75Gy}$ exceeds MS_{60Gy} Instrumental variable assumptions are met. $MS_{Proton75Gy}$ no different to $MS_{IMRT75Gy}$ $PRO_{Proton75Gy}$ superior to $PRO_{IMRT75Gy}$ $NCF_{Proton75Gy}$ superior to $NCF_{IMRT75Gy}$	p<0.15 (1-sided) p<0.15 (1-sided) p≥0.3 (2-sided) p<0.05 (2-sided)	Proton 75 Gy versus 60 Gy

APPENDIX VI (8/7/15)

Appendices for NRG Biospecimen Collection

NRG FFPE Specimen Plug Kit Collection
NRG Frozen Tissue Kit Instructions
NRG Blood Collection Kit Instructions
NRG Urine Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For ALL Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank

University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- Include all NRG paperwork in pocket of biohazard bag.
- Check that the Specimen Transmittal (ST) Form has the consent boxes checked off.
- Check that all samples are labeled with the NRG study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

- **FFPE Specimens:**
  - o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - o FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear the block shaking it might break during shipping.
  - o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

- **Frozen Specimens:**
  - o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified. If possible keep Serum, Plasma, and Whole Bloods in separate bags.
  - o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - o Send frozen specimens on dry ice via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80°C until ready to ship.

- **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

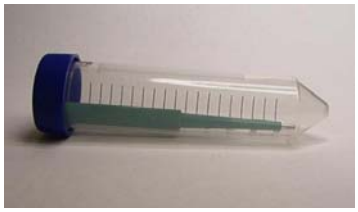
NRG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper pathology specimen ID and block ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
UCSF Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For ALL Frozen Specimens or Trackable shipments
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

NRG FROZEN TISSUE KIT INSTRUCTIONS

This Kit is for processing and shipping of frozen tissue specimens not embedded in OCT blocks. If the tissue is embedded in an OCT block, ship the block in an appropriate container on Dry Ice.

Kit contents:

- Biohazard pads/wipes 4" x 4" (orange)
- Five (5) 5-mL cryovials
- Disposable scalpel blades
- Disposable forceps
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Prepaid shipping label
- UN 3373 Label
- UN 1895 Dry Ice Sticker

Preparation and Processing of Fresh Frozen Tissue:

- On sterile cutting board, lay out the underpads.
- Keep biohazard wipes nearby to keep area clean throughout process.
- Label cryovials with NRG study and case numbers
- Using provided disposable scalpel, evenly cut tissue into 3 to 5 separate pieces (Note: if a frozen core was obtained, do not cut but send it whole).
- Use forceps to place each piece of tissue into individual 5-mL cryovials.
- Snap freeze tissue samples in liquid nitrogen, a dry ice slurry (dry ice with 95% ethanol or isopentane), or directly on dry ice.
- Once frozen, place all of the cryovials into biohazard bag
- Use NRG provided labels to label the bag (provided when patient is registered)..

Storage and Shipping:

Freezing and Storage

- Store at -80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- Include all NRG paperwork in pocket of biohazard bag.
- Place specimens and the absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7-10 lbs.—if appropriate; double-check temperature sample shipping temperature). Place Styrofoam cooler into outer cardboard box, and attach shipping label to outer cardboard box.
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.*
- Send frozen specimens via overnight courier to the address below. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays.
- Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen until ready to ship.
- For Questions regarding collection/shipping or to order a Frozen Tissue Kit, please contact the NRG Oncology Biospecimen Bank by **e-mail: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271**.

  Courier Address (FedEx, UPS, etc.): For ALL Frozen Specimens
  NRG Oncology Biospecimen Bank, University of California San Francisco
  2340 Sutter Street, Room S341, San Francisco, CA 94115

NRG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of <u>serum, plasma, or whole blood</u> *(as specified by the protocol)*:

<u>Kit contents</u>:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-five (25) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal (ST) Form and Kit Instructions

<u>PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD</u>**:**

(A) <u>Serum (if requested): Red Top Tube</u>

- Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the NRG study and case number, collection date, time, and time point, and clearly mark cryovials “serum”.

<u>Process</u>:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. Aliquot **<u>0.5 ml serum</u>** into as many cryovials as are necessary for the serum collected (5 to 10) labeled with NRG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90°C until ready to ship on dry ice. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.

(B) <u>Plasma (If requested): Purple Top EDTA tube #1</u>

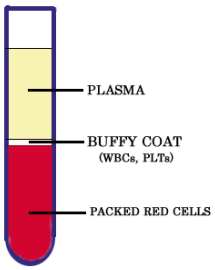
- Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the NRG study and case number, collection date, time, and time point, and clearly mark cryovials “plasma”.

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot **<u>0.5 ml plasma</u>** into as many cryovials as are necessary for the plasma collected (5 to 10) labeled with NRG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.

(continued on next page)

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.



(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot **1.0 ml blood** into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80 Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

Freezing and Storage:

- Freeze Blood samples in a -80 Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- Store at –80 (-70 to -90) until ready to ship.
  If a -80 Freezer is not available,
  - Samples can be stored short term in a -20 freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

(continued on next page)

Shipping/Mailing:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all NRG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.

Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard

- bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For ALL Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: NRGBB@ucsf.edu

NRG URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of urine specimens.

Kit Contents:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipettes
- Absorbent paper towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

Process:

- A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
  - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/cleansing wipes to remove any contaminants.
  - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
  - After 10-25 mL urine has been collected, remove the container from the urine stream without stopping the flow of urine.
  - Finish voiding the bladder into the toilet bowl.
- Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- Discard remaining Urine and collection cup.
- Label the specimen with the NRG study and case number, collection date and time, time point of collection, and clearly mark specimens as “urine”.
- Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C freezer until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED with NRG study and case numbers, collection date/time, and time point collected (e.g. pretreatment, post-treatment).

Storage and Shipping:

Freezing and Storage:

- Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  OR:

  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all NRG paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- Samples received thawed will be discarded, and a notification will be sent immediately to the Principal Investigator and Clinical Research Assistant of the submitting institution. The institution should send a subsequent sample, collected as close as possible to the original planned collection date.
- **For questions regarding ordering, collection, or shipping of a Urine Collection Kit, please e-mail RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271.**

Shipping Address: FedEx/UPS/Courier address (For ALL frozen samples)
NRG Oncology Biospecimen Bank at UCSF
2340 Sutter Street, Room S341, San Francisco, CA 94115
Contact Phone: 415-476-7864

APPENDIX VII (8/7/15)

CERTIFICATION AND ADMINISTRATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY

STEP 1 – EXAMINER CERTIFICATION FOR NRG-BN001

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

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

1) Read Section 11.3 of the protocol
2) Read this Appendix (Certification and Administration Procedures for the Neurocognitive Test Battery)
3) Go to the CTSU web site and use your username and password to access the link entitled, "Neurocognitive Training Procedure Letter". This letter will provide you with the web address and study specific password for the training video as well as the Training Video Post Test.
4) Obtain copies of the Neurocognitive Function Test packets (containing the HVLT-R, TMT and COWA), and the "Blank RAVE BN001 Forms" (containing the Neurocognitive Function Coversheet) from the CTSU website
5) Watch the training video
6) Complete the Training Video Post Test
7) Complete a "practice" assessment with the Neurocognitive Function Test packet
8) Complete the Certification Worksheet (Appendix IX)
9) All materials (i.e., Training Video Post Test, completed practice assessment with completed "Blank Rave BN001 Forms" pages that contain the Neurocognitive Function Coversheet, certification worksheet) must be scanned and emailed (NeuropsychologyResearch@mdanderson.org) or faxed (713-794-4999) to Dr. Wefel, who will review it and correct any procedural errors with the trainee.
10) If the trainee demonstrates competency, he/she will be notified of the certification approval to administer the tests to study subjects as part of NRG-BN001. A certification approval notice will be sent to CTSU for the registration process and to ensure that only NRG-BN001-approved examiners are testing subjects on protocol NRG-BN001.
11) **After you are certified, please scan and email (NeuropsychologyResearch@mdanderson.org) or fax (713-794-4999) all neurocognitive test and summary forms for the first study patient you test on NRG-BN001 to Dr. Wefel for centralized review.**

STEP 2 – NEUROCOGNITIVE TEST PACKETS

Two of the tests to be administered have alternate forms or versions in order to reduce the effects of practice. The tests have been grouped together in Packets that contain alternate versions of these neuropsychological tests. Please administer the tests in the order prescribed in the test packets. To ensure that the correct order is maintained per patient, please ensure that the NCF test packets are used

in the order provided. If for any reason neurocognitive testing was not performed at an applicable patient visit, please use the next sequential packet at the next applicable visit (ie
Patient Visit 1 = Packet 1, Patient Visit 2 = Packet 2, Patient Visit 3 = Packet 3 – or, if the second time point was missed – Patient Visit 1 = Packet 1, Patient Visit 2 = neurocognitive testing missed, Patient Visit 3 = Packet 2).

	≤ 28d prior to Step 2 Registration	72h prior to day 1 of cycle 4**	Day 25-28 of cycle 12**
NCF Packet	Packet 1	Packet 2	Packet 3

**Neurocognitive testing should be performed as close to the day of the contrast-enhanced MRI as possible

STEP 3 — TEST INSTRUCTIONS AND ADMINISTRATION PROCEDURES

Additional comments:

1. Testing must be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.
2. Tests should be administered in the following order to every patient and at every study visit: HVLT-R Part A (Trials 1-3); Trail Making Test Part A; Trail Making Test Part B; COWAT; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition).
3. You may fill the delay interval between COWA and HVLT-R Part B (Delayed Recall) with HRQOL and Symptom questionnaires.
4. Follow the instructions on the Forms Packet Index before submission of forms to NRG.
5. Please keep all original test forms. In the event of questions, contact Dr. Wefel. Copies of the test forms and summary sheets for the first case from each certified examiner must be scanned and emailed (NeuropsychologyResearch@mdanderson.org) or faxed for review to Dr. Wefel (713-794-4999). Additional test forms are not submitted to Dr. Wefel nor to NRG Headquarters. Results remain on file at the institution as source documentation pending request for submission by NRG or a study chair.
6. All test results are recorded in the RAVE system – see "Blank RAVE BN001 Forms" on the CTSU website for an example [this packet contains the Neurocognitive Function Coversheet]. 7. Patients should not be given copies of their tests to avoid learning the material between test administrations.
8. Before dismissing the patient, thank the patient for his/her cooperation.
9. In the event that a patient cannot complete a given test, please write the reason(s) on the test form AND the Neurocognitive Function Coversheet section of the RAVE forms.

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

This test has three parts and six alternate forms:
Part A - Free Recall: Complete the three learning trials first
Part B - Delayed Recall: Complete after a 20 minute delay that includes administration of Trail Making Tests and COWA as well as the symptom self-report measures if appropriate
Part C - Delayed Recognition: Complete immediately after Delayed Recall

Part A – Free Recall: 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.

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. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: 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. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: 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, 14:00) 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 and every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table).* Give the patient a 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 Test Data Sheet and the Neurocognitive Function Coversheet section of the RAVE forms. 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. Collect the worksheet and complete the Trail Making Data Sheet and the Neurocognitive Function Coversheet section of the RAVE forms indicating the reason the test was terminated and the last correct number reached on the test.
- If the patient successfully completes the test collect the worksheet and record the time to completion on the Trail Making Test Data Sheet and the Neurocognitive Function Coversheet section of the RAVE forms in minutes and seconds. Then say, "That's fine. Now we'll t***ry*** another one."

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

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

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

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their

hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
Examiner: "Now you try it. Remem***ber, begin at number 1 (*****point to 1*****) and draw a line from 1 to A (*****point to A*****), A to 2 (*****point to 2*****), 2 to B (*****point to B*****), B to 3 (*****point to 3*****) and so on, in order, until you reach the circle marked END (*****point**). Ready, begin."

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

Part B – Test:
After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:
Examiner: " Good! Let's try the next one. On this pag***e 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 fa***st as you can. Ready, begin."

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

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

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 and the Neurocognitive Function Coversheet section of the RAVE forms.

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 o**f 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 record sheet provides lines on which the patient's responses can be entered *(e.g., write in the word that is said by the patient)*. Record all patient responses verbatim. 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 and then initial and date in the margin next to the error.
- 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 on the recording sheet and on the Neurocognitive Function Coversheet section of the RAVE forms that is sent to the NRG.

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 *(for example, pasta; passé; lasagna)* can be counted as correct if they can be considered part of the lexicon of the relevant language, the criterion being their listing in a standard dictionary of that language. All incorrect and repeated responses MUST be crossed out with one single line, initialed and dated. Additionally, all duplicate entries that have been verified to have different meanings must be marked "ok", initialed and dated. 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 – you will also enter these on the Neurocognitive Function Coversheet section of the RAVE forms..

- ☐ If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Neurocognitive Function Coversheet section of the RAVE forms.

4. 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, 14:20) 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 HVLT-R. 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 lis***t?"

- ☐ 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 on the Neurocognitive Function Coversheet section of the RAVE forms.
- ☐ For this portion of the HVLT-R you will count the number of 'UPPER CASE' words answered "Yes" and record this number on the Neurocognitive Function Coversheet section of the RAVE forms. You will also count the number of 'lower case' words answered "Yes" and record this number on the Neurocognitive Function Coversheet section of the RAVE forms.

APPENDIX VIII (8/7/15)

ADVANCED MR IMAGE ACQUISITION PROTOCOL

Advanced MRI scans will be obtained at baseline and at subsequent follow-up time points at designated, approved sites on subjects identified and enrolled into the advanced imaging component.

For information on site qualification, contact the ACR Clinical Research Center at imagearchive@acr.org.

Advanced MR scans obtained at baseline prior to RT treatment and Wk.3 during chemo-radiation MRI scans are to be performed on the same magnet. The post-operative MR scan can also be used as the baseline MR scan as long as advanced imaging protocol guidelines are followed. Advanced MR scans obtained following chemo-radiation should be performed on the same magnet strength and vendor machine if at all possible.

** All advanced imaging cases should include the site's standard of care imaging for pre and post contrast brain.

Diffusion MRI Protocol

Recommended parameter ranges:

Isotropic DWI Series: Axial; FOV = 240mm; Acquisition Matrix =128x128 to 192x192 for an acquired in-plane resolution <1.87mm; ; Slice Thickness 4mm skip 0mm; Single-Shot Spin-Echo EPI; TR/TE = >5000ms/minimum; NSA = 1-2; Parallel Acceleration Factor=prefer 3 (3T systems) and prefer 2 on 1.5 T systems. B-factor=0,500,1000 sec/mm^2 on 3 orthogonal axes.

Pulse Sequence	Single-Shot Spin-Echo EPI
Plane	Axial
FOV	240mm
TR	>5000
TE	min
Slice thickness	<4mm
Gap	0
Acquisition Matrix	128x128-192x192
Acquired In-plane resolution	<1.87mm
NSA	>1
Parallel Acceleration Factor	2
b value factors	0,500,1000sec/mm on 3 orthogonal axes

Dynamic Susceptibility Contrast (DSC) MRI Protocol

Description

Leakage of Gd contrast into the interstitial space alters DSC signals and adversely affects perfusion values. A "pre-load" of at least 5cc of Gd contrast delivered approximately three minutes before the DSC scan will greatly mitigate this effect. This pre-load followed by DSC can be accomplished by acquisition of two identical DSC-MRI scans where one-quarter the total dose of contrast is administered in the first DSC scan and the remaining three-quarter dose in the second DSC scan, and the start of the two DSC scans are three minutes apart. Total Gd contrast dose is calculated by body weight. For example, a FULL body-weight dose of 0.1mmol/kg = 0.2cc/kg is 20cc of contrast for a 100kg patient, where 5cc of Gd contrast is administered for DSC scan#1 followed by 15cc of Gd contrast for DSC scan#2.

General technique

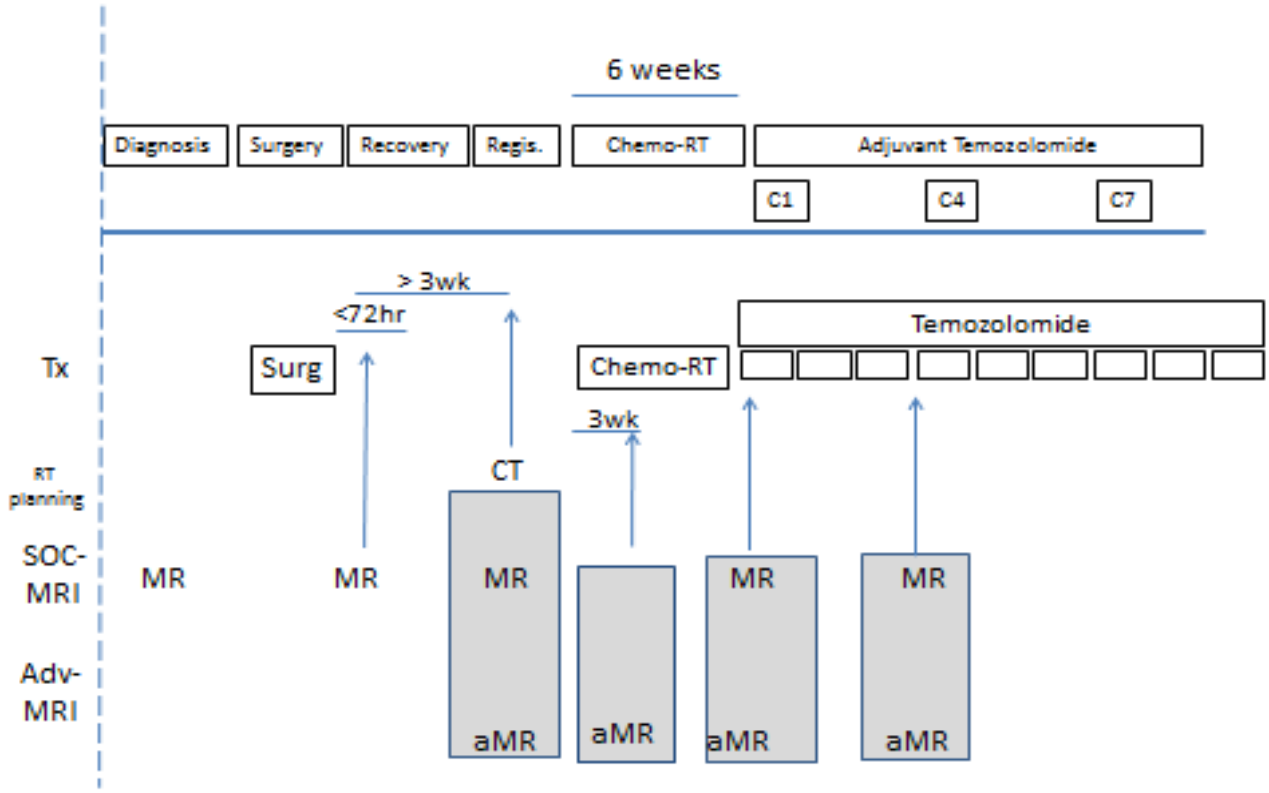
The single shot EPI sequence should be set up to collect 80 or more time points with a TR between 1.3 and 1.7 seconds. A GRE-EPI is suggested: For GRE-EPI, echo time (TE) should equal 30 to 40 milliseconds.

Specific DSC-MRI acquisition

- Start the first DSC-MRI sequence to obtain full coverage of the tumor volume.
- After collecting 20 baseline points, inject the bolus of contrast agent using one-quarter of the standard dose of 0.1 mmol/kg (up to 10cc) at a rate of $\geq$2 cc/sec rate followed by 15cc flush
- Continue collecting the data so that at least 60 more time-points are collected per slice.
- At the conclusion of the first DSC series, repeat the series using with the remaining three-quarter dose of the gadolinium.

Recommended Perfusion-Weighted Imaging Parameters

Pulse Sequence	2D EPI
Plane	Axial
TR	1.3 – 1.7 sec
TE(ms)	30-35
Repetitions	80-120
Flip Angle	60°
FOV	220-240mm
PFOV	100%
Sl. Thickness	4-6mm
Gap	0 to 2.5mm
Matrix	128x128
Phase Direction:	A-P


6 weeks
Diagnosis
Surgery
Recovery
Regis.
Chemo-RT
Adjuvant Temozolomide
C1
C4
C7
> 3wk
<72hr
Temozolomide
Tx
Surg
Chemo-RT
3wk
RT planning
CT
SOC-MRI
MR
MR
MR
MR
MR
Adv-MRI
aMR
aMR
aMR
aMR

APPENDIX IX (8/7/15)

CERTIFICATION WORKSHEET FOR TEST ADMINISTRATOR
NRG-BN001

This worksheet must be completed and signed by the person requesting certification and submitted to Dr. Wefel prior to the registration of any patients to NRG-BN001. Refer to Appendix VII for details.

_____ (Y) 1. Have you reviewed the Certification and Administration Procedures for the Neurocognitive Test Battery in Appendix VII of the protocol?

_____ (Y/N) 2. Have you completed the full certification to perform the neurocognitive battery testing for RTOG 0825, 0834, or 1114 during the past 6 months?

_____ (Y) 3. Have you watched the Neuropsychological Test Administration Video?

_____ (Y) 4. Have you completed and submitted the Training Video Post Test and a "practice" Neuropsychological Assessment with the Neurocognitive Function Coversheet section of the RAVE forms?

Institution CTEP ID/institution name:_____

Name of test administrator: _____

List any other applicable affiliated sites:
Institution CTEP ID/institution name:_____

Institution CTEP ID/institution name:_____

Institution CTEP ID/institution name:_____

Institution CTEP ID/institution name:_____

Telephone number of test administrator _____

Fax number of test administrator: _____

E-mail address of test administrator: _____

_____ _____
Signature of test administrator Date
(person who read Appendix VII, watched video and completed a post test and "practice" Assessment)

If you have any questions regarding the certification, please contact Dr. Wefel. Once you have completed this form, please attach both the Neuropsychological Function Test from the "practice" subject with the Neurocognitive Function Coversheet section of the RAVE forms and the Training Video Post Test and submit to:

Jeffrey S. Wefel, Ph.D.; Phone (713) 563-0514; FAX (713) 794-4999;
NeuropsychologyResearch@mdanderson.org

For Dr. Wefel's Use Only *(to email to* CTSURegOffice@ecogchair.org AND ctsucontact@westat.com *)*

_____(Y/N) The above individual has been certified to administer the neurocognitive tests for this study.

Signature_____Date_____

APPENDIX X (8/7/15)

CENTRAL LABORATORY ASSESSMENT FOR HYPERMETHLYATION OF THE PROMOTER OF THE O^6-METHYLGUANINE DNA METHYLTRANSFERASE (*MGMT*) GENE BY REAL-TIME PCR

MGMT Assay Description

The standard method for analysis of MGMT promoter methylation relies on methylation-specific PCR (MS-PCR) using bisulfite converted DNA. The assay was initially reported by Herman et al and is performed commercially in the United States by LabCorp under license from MDxHealth (Esteller et al., 2000a). The assay was utilized in the retrospective analysis of EORTC 22981 to demonstrate a benefit to MGMT promoter methylation for patients treated with concurrent TMZ and RT (Hegi et al., 2005). MGMT promoter methylation has been evaluated in two large, multicenter trials prospectively: the RTOG 0525 trial comparing standard dose vs. dose-dense TMZ in the adjuvant treatment of newly diagnosed patients with GBM (Gilbert et al., 2013) and the RTOG 0825 trial assessing the role of bevacizumab for patients with newly diagnosed GBM (Gilbert et al., 2014). Both trials stratified patients based on MGMT status using the same assay as that planned for the current study. For RTOG 0525, a total of 833 patients were randomized and MGMT status was determined to be hypermethylated in 245 tumors (29%), unmethylated in 517 tumors (62%). 91% of registered patients had tumors for which MGMT status could be determined. Median survival for methylated patients was significantly longer (22 months) as compared to the unmethylated patients (14 months). Similarly, for RTOG 0825, 621 patients were randomized and methylation status determined in 604 cases. A total of 175 (28%) were methylated and 429 (69%) were unmethylated. Median survival was 23.2 months vs. 14.3 months for the methylated vs. unmethylated patients. Based on these prospective, multicenter cooperative group trials, we anticipate MGMT methylation in approximately 30% of cases.

For this clinical trial, the MGMT assay will be performed as initially described by Esteller et al (Esteller et al., 1999) and as modified for real time PCR product detection. This approach yields a result identical to that used by LabCorp/MDxHealth. Following central pathology review by Dr. Aldape, a minimum of 5 unstained formalin-fixed, paraffin-embedded (FFPE) tumor sections will be obtained with areas of viable tumor identified. Slides will be processed by the MDACC CLIA MDL for prospective analysis of MGMT status. DNA will be prepared following deparaffinization. Bisulfite conversion of 1 µg of DNA will be performed (Zymo EZ96 DNA methylation kit, Zymo Research) and the remainder of tumor DNA will be frozen at -20C and kept for repeat analyses of MGMT if necessary and for future genomic analyses.

Amplification of bisulfite-modified DNA will encompass the standard enhancer region within the first intron of *MGMT* as previously described (Esteller et al., 2000b), generating a 136bp amplicon derived from positions 131155505-131155619 (RefSeq NM_002412) on chromosome 10. PCR primer sequences are as published (Vlassenbroeck et al., 2008). The assay detects the difference in amplification between methylated and unmethylated cytosine residues within the specific primer sequences. Conversion of unmethylated cytosines to uracil (thymidine) by sodium bisulfite treatment leads to a sequence change that can be detected using specifically designed PCR primers.

Amplification will be performed using real-time PCR in a Life Technolgies ViiA7 Fast Real-Time PCR system or equivalent, and detection will utilize the Power SYBR Green system (Life Technologies). A ΔC_T, defined as the difference in the cycle in which the detected amplification curve (on a log-linear plot) crosses an empirically determined between the *MGMT* amplicon and the reference *ACTB* amplicon. Control methylated and unmethylated DNAs will be used with each batch. A ΔC_T of less than 8 cycles (>256 fold difference) indicates the presence of promoter methylation. A ΔC_T >9 cycles will be coded as unmethylated. Cases with a ΔC_T between 8 and 9 will be considered indeterminate.

All reactions are carried out in triplicate from replicate bisulfite converted DNA preparations. Discordant results will be repeated (including bisulfite conversion when sufficient DNA is available). Cases in which discordant results persist after repeated assays or for which amplification fails secondary to poor quality DNA (or other technical reasons) will be coded as failures/no data.

Assay Validation

To validate the assay at MD Anderson using the assay described above, a set of primary GBMs with known MGMT status using the commercial MDxHealth-developed assay were evaluated for MGMT methylation. Validation was performed according to FDA Clinical Laboratory Improvement Amendment (CIIA) guidelines.

REFERENCES

Esteller, M., Garcia-Foncillas, J., Andion, E., Goodman, S. N., Hidalgo, O. F., Vanaclocha, V., Baylin, S. B., and Herman, J. G. (2000a). Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. N Engl J Med *343*, 1350-1354.

Esteller, M., Hamilton, S. R., Burger, P. C., Baylin, S. B., and Herman, J. G. (1999). Inactivation of the DNA repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation is a common event in primary human neoplasia. Cancer Res *59*, 793-797.

Esteller, M., Toyota, M., Sanchez-Cespedes, M., Capella, G., Peinado, M. A., Watkins, D. N., Issa, J. P., Sidransky, D., Baylin, S. B., and Herman, J. G. (2000b). Inactivation of the DNA repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation is associated with G to A mutations in K-ras in colorectal tumorigenesis. Cancer Research *60*, 2368-2371.

Gilbert, M. R., Dignam, J. J., Armstrong, T. S., Wefel, J. S., Blumenthal, D. T., Vogelbaum, M. A., Colman, H., Chakravarti, A., Pugh, S., Won, M.*, et al.* (2014). A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med *370*, 699-708.

Gilbert, M. R., Wang, M., Aldape, K. D., Stupp, R., Hegi, M. E., Jaeckle, K. A., Armstrong, T. S., Wefel, J. S., Won, M., Blumenthal, D. T.*, et al.* (2013). Dose-Dense Temozolomide for Newly Diagnosed Glioblastoma: A Randomized Phase III Clinical Trial. J Clin Oncol *31*, 4085-4091.

Hegi, M. E., Diserens, A. C., Gorlia, T., Hamou, M. F., de Tribolet, N., Weller, M., Kros, J. M., Hainfellner, J. A., Mason, W., Mariani, L.*, et al.* (2005). MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med *352*, 997-1003.

Vlassenbroeck, I., Califice, S., Diserens, A. C., Migliavacca, E., Straub, J., Di Stefano, I., Moreau, F., Hamou, M. F., Renard, I., Delorenzi, M.*, et al.* (2008). Validation of real-time methylation-specific PCR to determine O6-methylguanine-DNA methyltransferase gene promoter methylation in glioma. J Mol Diagn *10*, 332-337.