RADIATION THERAPY ONCOLOGY GROUP
RTOG 0925

NATURAL HISTORY OF POSTOPERATIVE COGNITIVE FUNCTION, QUALITY OF LIFE, AND SEIZURE CONTROL IN PATIENTS WITH SUPRATENTORIAL LOW-RISK GRADE II GLIOMA

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Institutions not aligned with RTOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- **The study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Members’ side of the website located at https://www.ctsu.org

- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.

- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.

- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to RTOG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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<td>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206</td>
<td>CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm.]</td>
<td>RTOG Headquarters 1818 Market Street, Suite 1600 Philadelphia, PA 19103 1-800-227-5463, ext. 4189 See Protocol Section 12 for data submission details. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
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For patient eligibility or treatment-related questions Contact the Study PI of the Coordinating Group.

For questions unrelated to patient eligibility, treatment, or 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.

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The CTSU Web site is located at: https://www.ctsu.org

CTSU logistical information is located in Appendix VIII.
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RADIATION THERAPY ONCOLOGY GROUP

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SCHEMA

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Patient Population: (See Section 3.0 for Eligibility)
Central pathology-confirmed diagnosis of supratentorial grade II oligodendroglioma, astrocytoma, or mixed oligoastrocytoma prior to Step 2 registration. The patient must be within one of the following categories:
- Maximal safe resection with minimal residual disease defined as follows:
  - Removal of T2/FLAIR abnormalities thought to be primarily tumor, with a residual ≤ 2 cm maximal tumor diameter/T2 FLAIR abnormality on MRI to be done within 84 days post-operatively.
  - If there is > 2 cm post-operative residual T2/FLAIR abnormality and the neurosurgeon believes this represents edema and not primarily tumor; the neurosurgeon is encouraged to repeat imaging within the allowed study period (up to 84 days post-operatively) to confirm resolution of edema. MRI at the time of enrollment must document a ≤ 2 cm residual maximal tumor diameter/T2 FLAIR abnormality.
  - Patients who required a second surgery to obtain a maximal safe resection will be eligible if the second surgery is performed within 84 days of the initial diagnostic procedure.
- OR
  - Age <40 (any extent of resection)
- OR
  - Age < 50, preoperative tumor diameter < 4 cm (any extent of resection)

Required Sample Size: 170 patients
1. Is the patient suspected to have supratentorial grade II oligodendroglioma, astrocytoma, or mixed oligoastrocytoma? (Y)

2. Is Step 1 registration occurring within 84 days from most recent surgery? (Y)

The following questions will be asked at Study Registration for STEP 1:

1. Institutional person randomizing case.
2. Has the Eligibility Checklist been completed? (Y)
3. In the opinion of the investigator, is the patient eligible? (Y)
4. Date informed consent signed
5. Patient’s Initials (First Middle Last)
6. Verifying Physician
7. Patient ID
8. Date of Birth
9. Race
10. Ethnicity
11. Gender
12. Country of Residence
13. Zip Code (U.S. Residents)
14. Method of Payment
15. Any care at a VA or Military Hospital?
16. Calendar Base Date (The Calendar Base Date is the date the patient is registered)
17. Randomization date
1. Has central pathology-confirmed diagnosis of supratentorial grade II oligodendroglioma, astrocytoma, or mixed oligoastrocytoma prior to Step 2 registration?

2. Is there no evidence of multifocal disease, based upon the following minimum diagnostic work-up:
   - History/physical examination, including neurologic examination, within 84 days prior to Step 2 registration
   - Brain MRI with and without contrast within 84 days prior to Step 2 registration (Note: MRI 70 days after surgery is preferred and highly encouraged)

3. Is the patient’s age ≥ 18?

4. Does the patient have one of the following categories:
   Maximal safe resection with minimal residual disease defined as follows:
   - Removal of T2/FLAIR abnormalities thought to be primarily tumor, with a residual ≤ 2 cm maximal tumor diameter/T2 FLAIR abnormality on MRI to be done within 84 days post-operatively.
   - If there is > 2 cm post-operative residual T2/FLAIR abnormality and the neurosurgeon believes this represents edema and not primarily tumor; the neurosurgeon is encouraged to repeat imaging within the allowed study period (up to 84 days post-operatively) to confirm resolution of edema. MRI at the time of enrollment must document a ≤ 2 cm residual maximal tumor diameter/T2 FLAIR abnormality
   - Patients who required a second surgery to obtain a maximal safe resection will be eligible if the second surgery is performed within 84 days of the initial diagnostic procedure.
   - OR
   - Age < 40 (any extent of resection)
   - OR
   - Age < 50 and preoperative tumor diameter < 4 cm (any extent of resection)

5. Does the patient have a 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)?

6. Is the patient unable to undergo MRI of the brain with gadolinium?

7. Does the patient have a recurrence for this tumor?

8. Has the patient received prior surgery, chemotherapy, and/or radiation therapy for this tumor?
The following questions will be asked at Study Registration for STEP 2:

1. Institutional person randomizing case.

2. Is the patient eligible to participate in the protocol?

   _____ If no, provide the reason the patient cannot continue:
   1. Insufficient tissue
   2. Checklist failure: specify __________________
   3. Progression of disease.
   4. Patient refusal.
   5. Physician preference
   6. Death
   7. Toxicity
   8. Other complicating disease
   9. Other, specify ____________________________

3. Patient’s Initials (First Middle Last)

4. Verifying Physician

5. Patient ID

6. Calendar Base Date

7. Randomization date

8. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

9. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

10. Have you obtained the patient's consent for his or her urine to be kept for use in research to learn about, prevent, treat, or cure cancer?

11. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

12. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

13. Have you obtained the patient's consent for his or her urine to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

14. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by ___________________________ Date ___________________________
1.0 INTRODUCTION

Optimal therapy for patients with low-risk, supratentorial grade II glioma remains a highly controversial issue in the neuro-oncology community. Recent phase II data from RTOG 9802 show that, although the 2-year and 5-year overall survival (OS) rates in low- (99% and 93%) versus high-risk (87% and 66%) low-grade glioma (LGG) were significantly different (P<0.0001), the progression-free survival (PFS) was not (82% and 48% vs. 73% and 50%, with P =0.13) (Shaw 2008). Because none of the current treatment modalities have been shown to improve OS (van den Bent 2005; Shaw 2008) observation is usually recommended in this “low-risk” population, even with this high rate of progression over time. Concerns regarding the toxicity of therapy are generally felt to outweigh the benefits of delaying tumor progression. In this group of young and highly functional patients, whose median survival can exceed 10 years (Schomas 2009). However, the recommendation for observation is made with little knowledge of the impact of radiological tumor progression on the quality of life (QOL), seizure control, cognitive function, and functional status of these patients. In addition, knowledge about the predictive role molecular markers play in predicting progression is scarce.

To better assess the clinical impact and meaning of tumor progression and whether observation is a reasonable strategy for low-risk LGG, this phase II trial will evaluate neurocognitive function (NCF), QOL, and seizure control over time and after tumor progression in patients undergoing observation alone after newly diagnosed LGG.

LGG compromises about 20% of all central nervous system (CNS) glial tumors. Approximately 2000 patients in the United States are annually diagnosed with LGG. Since the 1970s, prognosis for LGGs has significantly improved. This improvement is largely due to earlier diagnosis by the MRI scan, increased awareness of the more favorable oligo component, and stratification for young age. Because of the indolent natural history, multiple areas of controversy exist regarding the best approach to the management of LGG. Such controversies include the timing of surgery (immediate versus delayed intervention) (Recht 1992; Reijneveld 2001), the timing of radiation therapy (immediate versus deferred until time of progression) (van den Bent 2005), and the effects of radiation upon NCF (Laack 2005).

Despite their indolent natural history, with time these tumors invariably undergo malignant transformation. In an attempt to understand the natural history of low-risk LGG, RTOG 9802 was designed as a phase II/III study to stratify LGGs into low- (phase II observational arm) versus high- (phase III) risk groups, with observation for the former and radiation plus post-radiation PCV chemotherapy for the latter. Approximately 44% of the patients enrolled in this study were eligible for the low-risk trial (111 versus 251). Although the OS was superior for low-risk LGG, the PFS showed no significant difference (Shaw 2008). Data from this prospective randomized RTOG trial established observation as an acceptable, but not necessarily superior, standard of care in this group of low-risk patients; the best standard of care remains largely unestablished. Likewise, EORTC 22845 was a randomized trial looking at the long-term efficacy of early versus delayed radiotherapy for all comers with LGG in adults. The median OS in early versus delayed radiation showed no statistically significant difference (7.1 versus 7.9 years), with median PFS of 5.4 years versus 3.7 years (p= 0.003). One possible benefit of early radiation was better seizure control at 1 year post-radiotherapy (seizures present in 25% and 41% respectively) (van den Bent 2005). Seizure control was evaluated over the period of only 1 year rather than longitudinally, and NCF and QOL were not evaluated on this study. Current recommendations are often made by anecdotal experience or data from non-randomized, retrospective series. Because of concerns of late cognitive effects of radiotherapy, timing of radiotherapy is still controversial as some neuro-oncologists do not feel the benefits in PFS outweigh the risks of treatment.

Despite their low-grade histological characteristics, LGGs demonstrate varying degrees of molecular signatures and biological behaviors, with significant implications for patient care and outcomes. Additionally, despite their prolonged period of radiologic stability and slow clinical deterioration, they eventually undergo malignant transformation to a higher-grade glioma (Olson 2000; Recht 1992). The proposed prognostic features, which did not include surgical resection, have largely been gleaned from retrospective analysis by the European Organization for Research and Treatment of Cancer [EORTC] (Pignatti 2002). Inclusion of age as a favorable prognostic factor at diagnosis has been confirmed by a review from the SEERs data, with an 86% 10-year survival rate for age < 20, 53% for age 20 to 60, and 20% at age > 60 (Claus 2006). Recent single- and multi-institution retrospective reports also suggest certain subgroups exist with a more favorable OS. Schomas and coworkers (2009) from the Mayo Clinic report on a series of 400 patients with more than 13 years of follow-up. Patients who were able to
undergo a near-total or gross-total resection experienced a median survival of over 12 years. Support for
the favorable prognostic contribution of maximal safe resection remains as consensus opinion (Schomas
2009). This is consistent with the results from the low-risk cohort in RTOG 9802, in which patients with ≤ 2
cm residual disease had improved PFS compared to patients with > 2 cm postoperative residual disease
(Shaw 2008). In an important article by Chang et al (2008) from the University of California, San
Francisco, 4 preoperative prognostic factors were found to predict survival in a series of 281 patients from
their institution. In their series, tumor size (< 4 cm versus > 4 cm), tumor location (non-eloquent versus
eloquent), age (< 50 versus > 50), and Karnofsky performance status (KPS) ≥ 80 were found to be highly
predictive of OS. Patients with 0 to 2 of these risk factors experienced a median survival > 10 years
(Chang 2008). These data were subsequently validated by an outside multi-institutional series of patients
and are currently being used to guide treatment decisions in newly diagnosed LGG patients (Chang
2009).

Histological subtype is increasingly being recognized as an important prognostic factor. The
oligodendroglial subtype has been shown in many series to be associated with improved OS and PFS
(Schomas 2009; Pignatti 2002; Shaw 2002; Shaw 2008). Recent cytological studies including fluorescent
in-situ hybridization (FISH) for chromosomal analysis support the loss of 1p and 19q as a predictor of
favorable OS in LGG. Initially determined to be a prognostic factor in anaplastic oligodendrogliomas, it
appears to also be prognostic in LGG and is more commonly associated with the oligodendroglial cell
subtype. Currently, there is no molecular data from prospective clinical trials that would predict either
radiological tumor recurrence or malignant transformation in this group of good-prognosis brain tumors.
Such information is needed to guide clinical decision-making and further individualized therapy
recommendations in this heterogeneous group of patients.

Currently there are no uniformly accepted radiological criteria for defining disease progression or gross
total resection (GTR) in patients with diffusely infiltrating LGG. In 1990, Macdonald et al proposed the
universally accepted radiological criteria for defining disease progression in patients with enhancing
malignant grade III and grade IV gliomas (Macdonald 1990). As such, the Macdonald criteria do not apply
to patients with non-enhancing LGGs. There is an ongoing work in progress by an international working
group to define GTR and radiological progression in non-enhancing LGGs (van den Bent 2009). In
RTOG 9802, the primary investigator reviewed all MRIs and progression was defined as a “clear”
increase in the size of the T2 abnormality. Based on this definition, PFS was similar in the high-risk and
low-risk arms of the study. However, no correlation was performed between radiographic progression
and clinical outcomes. Specifically, it is unknown if patients with radiographic progression by this
definition experience any neurologic, neurocognitive, or symptomatic decline. In addition, because this
radiographic definition defines progression after fairly minimal growth, progression may not lead to
therapeutic intervention. Finally, this definition of progression did not correlate with OS (as evidenced by
the difference in survival between the low-risk and high-risk cohorts). Standardized and clinically
meaningful definitions of progression are clearly needed to further the study and understanding of these
tumors.

While efforts in clinical research have largely addressed issues of treatment and survival, symptom
management has largely been ignored in prospective clinical trials of LGG. Recent literature suggests
tumor effects may be the most significant factor associated with cognitive function; specifically, tumor
progression is more detrimental to cognitive function than most treatment-related variables (Laack 2004;
Laack 2005; Klein 2002). Neurocognitive status has been shown to be of predictive prognostic value in
patients with recurrent malignant glioma (Meyers 2000). Moreover, decline in neurocognitive status
during treatment has also been shown to be predictive of treatment failure long before any radiological,
clinical, or health-related quality of life (HRQOL) deterioration (Meyers 2003). This study will be the first
to attempt to correlate neurocognitive changes with radiologic, neurologic, and symptomatic progression
in LGG patients. Although vague radiographic definitions are currently used as the standard
determination of progression in LGG, it is unknown if radiographic changes are predictive of the cognitive,
neurologic, and QOL outcomes that are important to patients. Understanding the neurocognitive changes
caused by the tumor may help guide treatment decisions in the future by determining sub-groups in which
early treatment may delay time to cognitive decline or groups in which therapeutic intervention can be
further delayed with little risk of tumor-induced cognitive decline.

Seizures are prevalent and important symptoms in patients with LGG. It is estimated that 86% of patients
with LGG will have seizures at some time in their life, compared to 69% with anaplastic gliomas and 49%
with glioblastomas. No prospective data exist on the impact of seizure control upon survival, QOL, NCF, or cost of care (Lote 1998). Radiotherapy has been shown to reduce seizure frequency and improve seizure control in prospective trials (van den Bent 2005). Also, antiepileptic medications have been associated with cognitive dysfunction in LGG patients (Klein 2002). Although NCF is the primary endpoint in this study, and although antiepileptic medications do impact NCF, it is important to keep in mind that in this study each patient’s NCF will be its own control. Additionally, further investigation into the impact of seizure control is necessary to guide treatment decisions in this risk group.

Neurocognitive status plays a very important role in neuro-oncologic practice and clinical trials. The combination of limited therapeutic success and the effects of the tumor and its treatment upon emotional, cognitive, and behavioral function have led to consideration of HRQOL and NCF as outcome endpoints in addition to the traditional clinical and radiological endpoints. This respective combination of patient-centered and disease-centered outcomes becomes very important in the comparative assessment of new therapies, especially when survival-equivalent therapies result in different neurocognitive and HRQOL outcomes.

QOL has become recognized as a critical endpoint in clinical oncology trials. This is particularly the case in the setting of patients with a difficult prognosis, such as a low-grade brain tumor. QOL measures provide patient-derived information by which to analyze the delicate balance between the potential for improved survival and increased toxicity with experimental therapies. There is little prospective QOL data on patients with brain tumors and even less of this data over the course of the illness, which is often 5 years or greater. It is particularly important to obtain the patient’s perspective on his or her QOL, as previous research suggests that proxies such as health providers rate QOL better than QOL ratings from the patient and family (Sneeuw 1997). QOL evaluation in this study will help describe the impact of observation over time as well as the impact of tumor progression on QOL by comparing QOL between progressors and non-progressors. Further understanding of determinants of QOL in this population can guide decisions such that patients with significant QOL decline may benefit from earlier intervention.

An additional metric that would help inform future studies of the treatment of this disease is the quality adjusted life year (QALY). Measurement of outcomes such as PFS and the most important aspects of human functioning and QOL will permit a summary equation, allowing for differences in QOL and clinical outcomes into a single equation: the QALY. Health status and health-related quality of life were assessed by the Health Utilities Index 2 (HUI; McMaster University, Hamilton, Canada) in adults diagnosed with brain tumors (McCarter 2006). A decrease in utilities of 0.1 self-care single-attribute utility score was associated with an increased hazard of 30% in patients with low-grade tumors. The HUI is a multi-attribute health classification system that is administered to patients to determine utilities. This system is complex and time consuming to administer. For this study, the brief 5-item EuroQol (EQ-5D) will be utilized as an adjustment to survival. The EQ-5D instrument is a method for obtaining valuations (utilities) of HRQOL. Developed in 1987, the EQ-5D is used by investigators and the pharmaceutical industry throughout the United States, Europe, and Asia to assess both QALYs and cost-effectiveness. The EQ-5D instrument is intended to complement other forms of QOL measures, and it has been purposefully developed to generate a generic cardinal index of health, thus giving it considerable potential for use in comparing QALYs across and within diseases.

To better assess the impact of tumor progression and whether observation is a reasonable strategy for low-risk LGG, we propose a phase II trial that evaluates NCF, QOL, and seizure control over time and after tumor progression. For the purpose of this study, low-risk LGG is defined as patients having good prognosis and for whom current clinical practice is observation. This study seeks to compare NCF, QOL, and seizure control over time in untreated patients who have radiographic progression versus no evidence of radiographic disease progression. The finding of this study should help guide future treatment decisions in low-risk LGG patients such that if a significant decline in NCF over time is documented, earlier therapeutic intervention may be justified. In addition, future studies will benefit from a standardized method of defining progression in these patients, and clinicians will have more clinically meaningful outcomes on which to base treatment decisions. The long-term translational studies as well the exploratory progression endpoints will help clinicians decide if future patients should be treated at the time of first radiographic progression or if another endpoint is more important in predicting patients at risk for early symptomatic tumor progression despite the “low-risk” nature of this subset of LGG patients.
2.0 OBJECTIVES

2.1 Primary Objective
To determine if there is difference in the average changes of neurocognitive function (NCF) scores from baseline to the time of radiologic tumor progression or up to 5 years (whichever occurs first), between radiologically progressed and non-progressed patients.

2.2 Secondary Objectives
2.2.1 To determine if there is difference in the time to neurocognitive decline, as defined by the RCI-WSD (denotes: Reliable change index -- within-subjects standard deviation), between radiologically progressed and non-progressed patients.
2.2.2 To evaluate NCF during the postoperative observational period of progression-free survival (PFS) and after radiological progression for a total time on study of 5 years.
2.2.3 To determine if the changes in cognitive functioning are an early warning biomarker for radiological progression.
2.2.4 To explore the effect of salvage therapy on cognitive outcomes in patients who progress during the study period for up to 5 years.
2.2.5 To evaluate QOL as measured by the EORTC QOL-30 and QOL BCN20 brain module and health utilities as measured by the EQ-5D, for a total time on study of 5 years.
2.2.6 To evaluate seizure control for a total time on study of 5 years.
2.2.7 To evaluate molecular correlates of QOL, NCF, seizure control, and PFS.
2.2.8 To characterize aberrant molecular pathways in LGGs and test the hypothesis that activation of signaling pathways will predict worse PFS and overall survival (OS).
2.2.9 To explore the relationship between change in cognitive function and symptomatic progression (defined as worsening seizures or new or progressive neurologic deficits) or clinical progression (defined as initiation of treatment interventions such as radiotherapy, chemotherapy, or additional surgery).

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

3.1 Conditions for Patient Eligibility (8/15/13)
For questions concerning eligibility, please contact RTOG Data Management (via the RTOG contact list on the RTOG website) or the Study Chair (see first page of protocol).

3.1.1 Central pathology-confirmed diagnosis of supratentorial grade II oligodendrogloma, astrocytoma, or mixed oligoastrocytoma prior to Step 2 registration
3.1.2 No multifocal disease, based upon the following minimum diagnostic work-up
3.1.2.1 History/physical examination, including neurologic examination, within 84 days prior to Step 2 registration
3.1.2.2 Brain MRI with and without contrast within 84 days prior to Step 2 registration (Note: MRI 70 days after surgery is preferred and highly encouraged)
3.1.3 KPS ≥ 80
3.1.4 Age ≥ 18
3.1.5 Step 1 registration must occur within 84 days from most recent surgery
3.1.6 The patient must be within one of the following categories:
3.1.6.1 Maximal safe resection with minimal residual disease defined as follows:
   ▪ Removal of T2/FLAIR abnormalities thought to be primarily tumor, with a residual ≤ 2 cm maximal tumor diameter/T2 FLAIR abnormality on MRI to be done within 84 days post-operatively.
   ▪ If there is > 2 cm post-operative residual T2/FLAIR abnormality and the neurosurgeon believes this represents edema and not primarily tumor; the neurosurgeon is encouraged to repeat imaging within the allowed study period (up to 84 days post-operatively) to confirm resolution of edema. MRI at the time of enrollment must document a ≤ 2 cm residual maximal tumor diameter/T2 FLAIR abnormality
   ▪ Patients who required a second surgery to obtain a maximal safe resection will be eligible if the second surgery is performed within 84 days of the initial diagnostic procedure.
   OR
3.1.6.2 Age < 40 (any extent of resection)
   OR
3.1.6.3 Age < 50 and preoperative tumor diameter < 4 cm (any extent of resection)
3.1.7 Patient must provide study-specific informed consent prior to Step 1 registration.
3.1.8 No plans for adjuvant radiotherapy or chemotherapy after surgery. This is an observational trial.

3.2 Conditions for Patient Ineligibility (8/15/13)
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 Inability to undergo MRI of the brain with gadolinium;
3.2.3 Recurrence for this tumor;
3.2.4 Prior surgery, radiation therapy, and/or chemotherapy for this tumor.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT
NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management
Completion of the quality of life measurements [EORTC Quality of Life Questionnaire-Core 30 (QOL-30), the Brain Cancer Module-20 (BCM20), and the EQ-5D] is mandatory for this protocol. Institutions must administer the baseline (and follow-up) assessments for the QOL-30, the BCM20, and the EQ-5D.

5.0 REGISTRATION PROCEDURES
5.1 Pre-Registration Requirements for Neurocognitive Function Testing (10/4/11)
Institutions must meet certification requirements for administering neurocognitive assessments.

See Appendices IV and V for full certification requirements, and see Section 11.2 for How To Get Started With CogState overview.

NOTE: RAs credentialed for RTOG 0933 need to be credentialed for RTOG 0925.

5.2 Regulatory Pre-Registration Requirements (12/3/12)
5.2.1 All institutions must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, https://www.ctsu.org/public/CTSU-IRBcertif_Final.pdf. The study related regulatory documentation may also be e-mailed to the CTSU at CTSURegulatory@ctsu.Coccg.org. This must be done prior to registration of the institution’s first case:
- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification of consent translation to RTOG Headquarters
- IRB/REB assurance number

Non-English Speaking Canadian and International Institutions
Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved RTOG 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.

5.2.2 Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS
5.2.2.1 For institutions that do not have an approved LOI for this protocol:
International sites must submit an LOI to RTOG Headquarters to receive approval to participate in this trial. For more details see link below:
http://www.rtog.org/Researchers/InternationalMembers/LetterofIntent.aspx
5.2.3.2  **For institutions that have an approved LOI for this protocol:**
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.3  **Summary of Registration Procedures (3/22/12)**
Once the patient has been determined to meet pre-registration requirements, this study incorporates a 2-step registration process.

**Step 1** of registration entails an initial registration for central review of tissue for histologic confirmation.
- The site will register the patient and will then submit tissue to the RTOG Biospecimen Resource (see Section 10). A Pathology Screening Form (P4), pathology materials, and pathology report must be submitted to the Biospecimen Resource per Section 10.
- The RTOG Biospecimen Resource will forward the materials to Dr. Arie Perry at UCSF, who will perform the central review.
- Dr. Perry will evaluate the tissue to confirm histology and will notify RTOG Headquarters and the site of the results.
- If the histology is supratentorial grade II oligodendroglioma, astrocytoma, or mixed oligoastrocytoma the site may proceed to Step 2 registration, to register the patient for protocol intervention.
- If the histology is not supratentorial grade II oligodendroglioma, astrocytoma, or mixed oligoastrocytoma the site should complete Step 2 registration, to decline protocol intervention.
- If the patient does not proceed to protocol intervention despite histologic confirmation, Step 2 of registration must be completed, to decline protocol intervention.
- See Section 5.4 for online registration procedures.

**Step 2** of registration entails a second registration for initiating or declining protocol intervention.
- If applicable, a new data submission calendar will be generated at this time.
- See Section 5.4 for online registration procedures.

5.4  **Online Registration (12/3/12)**
Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:
- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via [http://phrp.nihtraining.com/users/login.php](http://phrp.nihtraining.com/users/login.php)).
- A representative from the institution must complete the Password Authorization Form at [http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219](http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219) and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site ([http://www.rtog.org](http://www.rtog.org)), going to “Data Center Logon” and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient’s record. Two e-mails are
generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study’s database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr.org or 800-227-5463 ext. 4189 or 215-574-3189.

In the event that the RTOG web registration site is not accessible, participating sites can contact RTOG web support for assistance with web registration: websupport@acr.org or call the RTOG Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site’s user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY
Not applicable to this protocol.

7.0 DRUG THERAPY
Not applicable to this protocol.

8.0 SURGERY
Not applicable to this protocol.

9.0 OTHER THERAPY
Not applicable to this protocol.

10.0 TISSUE/SPECIMEN SUBMISSION

NOTE: Patients must be offered the opportunity to participate in tissue/specimen submission component of this study.

- 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 RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource 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 RTOG Biospecimen Resource 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 RTOG Biospecimen Resource for the purpose of central review of pathology (mandatory for eligibility prior to Step 2 registration), tissue banking, and translational research (highly recommended).

10.2 Tissue Submission for Central Review (mandatory prior to Step 2 registration) (8/15/13)

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.2.1 All representative H&E stained slides from each block (slides can be a duplicate cut stained H&E; they do not have to be the diagnostic slide). One H&E is not sufficient for central review.

NOTE: These are essential for review as well as rapid turnaround time. Additionally, if the submitted block is deemed inadequate, the central reviewer will be able to identify a more
appropriate block. For patients participating in translational studies (see Section 10.3), one slide will be retained by RTOG. The remainder of all H&E slides will be returned to the submitting institution once central review is complete.

10.2.2 Special stains, if available.
10.2.3 One Representative tumor block, formalin-fixed preferred (the block must match one of the H&E slides being submitted).

**NOTE:** If the submitted block is deemed inadequate, the central reviewer will be able to identify a more appropriate block from the other H&Es that were submitted for central review. If a tumor block is not available, 6 unstained 5μm tumor tissue sections on charged slides may be used. All 7 slides (1 H&E and 6 unstained) are to be consecutively cut from the representative block. Materials must be from blocks that have not been frozen. For patients participating in translational studies, blocks will be retained by RTOG (see Section 10.3).

10.2.4 A Pathology Report documenting that the submitted block contains tumor. The report must include the RTOG protocol number and patient’s case number. 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.

- The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.2.5 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient’s case number.

10.2.6 A study-specific Pathology Screening Form (P4) must be completed by the local pathologist and must be included in the central review pathology submission.

10.2.7 Central review will be performed for every case by Dr. Arie Perry within 10 business days of receipt from the Biospecimen Resource; in general, the Biospecimen Resource will send slides (or images of the slides) to Dr. Perry within 1-2 business days of receipt and within 3 business days if an H&E slide has to be made when only the block is submitted. Upon receipt of tissue for central review, the RTOG Biospecimen Resource will forward tissue to Dr. Perry. After the central review is complete, Dr. Perry will notify RTOG Headquarters and the site of the results and will then: (1) return remaining tissue to the RTOG Biospecimen Resource for banking and translational research for consenting patients; or (2) return remaining tissue to the site for non-consenting patients.

10.3 Specimen Submission for Banking and Translational Research (Highly Recommended) (8/15/13)

10.3.1 Tissue Collection
10.3.1.1 Dr. Perry will return tissue remaining after central review completion to the RTOG Biospecimen Resource per Section 10.2.8.

10.3.1.2 To ensure enough tissue for the translational aims of the study, at least 1 cubic centimeter of tissue composed primarily of tumor should be submitted. As specified in Section 10.2, one tumor block will be retained after central review for patients participating in the translational components of the study and sent to Dr. Joanna Phillips at UCSF for translational studies.

10.3.2 Plasma, Whole Blood, and Urine Collection
Plasma, whole blood and urine will be collected pretreatment. For collection and shipping instructions see Appendix VI.

**See Appendix VI for detailed biospecimen collection and preparation instructions, including information pertaining to collection kits. Kits can be requested from the Biospecimen Resource by email.** [rtog@ucsf.edu](mailto:rtog@ucsf.edu).

**Note:** Kits include a pre-paid overnight courier label for shipping of Frozen samples.

A Specimen Transmittal Form documenting the date of collection of the biospecimen; the collection timepoint, RTOG protocol number, the patient’s case number, and method of storage, for example, stored at -20°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).

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

**OR:**
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

### 10.3.4 Specimen Collection Summary

<table>
<thead>
<tr>
<th>Specimens for Tissue Banking/Central Review/Translational Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimens taken from patient:</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Central Review (Mandatory)</strong></td>
</tr>
<tr>
<td>H&amp;E stained slides: one from each block</td>
</tr>
<tr>
<td>One representative tumor block, formalin-fixed preferred.</td>
</tr>
<tr>
<td>H&amp;E slide from the submitted representative tumor block.</td>
</tr>
<tr>
<td>Special stains if available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Specimens for Banking and Translational Research (Highly Recommended)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimens taken from patient:</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>H&amp;E stained slide from representative tumor block</td>
</tr>
<tr>
<td>One tumor block, formalin-fixed preferred. Ideally 1 cubic centimeter of tissue, composed primarily of tumor</td>
</tr>
<tr>
<td>PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge</td>
</tr>
<tr>
<td>Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix</td>
</tr>
<tr>
<td>10-20 mL clean-catch urine</td>
</tr>
</tbody>
</table>
10.3.5 Submit materials for Tissue Banking, Central Review, Translational Research as follows:

U. S. Postal Service Mailing Address: For Non-frozen/Non-urgent Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
UCSF Box 1800
2340 Sutter St, room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Central Review FFPE Samples and Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

Questions: 415-476-RTOG (7864)/FAX 415-476-5271; RTOG@ucsf.edu

10.4 Translational Research (Highly Recommended)

10.4.1 Rationale

Over the past few years, several key discoveries related to LGG biology have been made. Notably, in approximately 60% of astrocytomas, there is inactivation of the TP53 locus, while in over 80% of oligodendrogial lesions there is allelic loss of chromosome 1p and 19q (Rasheed 1994; Reifenberger 1994). Both variants can also exhibit overexpression of the platelet derived growth factor (PDGF) and its receptor (Varela 2004; Mairi 2006). 1p/19q status in oligodendrogliomas also appears to correlate with promoter methylation of the DNA repair enzyme O6-Methylguanine-DNA methyltransferase (MGMT); in patients with 1p/19q deletions, upwards of 85% have concomitant MGMT methylation (Molleman 2005). This study will be important in prospective documentation of molecular markers (1p, 19q, P53, MGMT) at initial diagnosis as well as at time of progression.

In addition, a recent study found PTEN hypermethylation in upwards of 50% of grade II astrocytomas, oligodendrogliomas, and mixed histology tumors. Whereas mutation of PTEN is common in de novo malignant gliomas (Rasheed 1997; Ermoian 2002; Choe 2003), methylation of the PTEN promoter may be an underlying mechanism of PTEN alteration found in LGGs and secondary malignant gliomas (Wiencke 2007). Whereas there is no evidence of PTEN promoter methylation in normal brain and only 9% methylation in de novo glioblastomas, low-grade tumors displayed methylation of PTEN promoter in 43% to 67% of cases, and in 68% to 82% of secondary high-grade gliomas. The differences in PTEN promoter methylation frequencies for LGGs were highly statistically significant (P<0.001) (Wiencke 2007).

Not only is methylation of the PTEN promoter frequent and associated specifically with LGG and secondary malignant gliomas, there is evidence that PTEN methylation also leads to functional activation of the PI3K pathway, a pathway that is thought to be important for tumor transformation and growth (Wiencke 2007). A recent retrospective study of 45 newly diagnosed LGGs sought to evaluate whether activation of the PI3K pathway correlates with survival by examining expression patterns of proteins within this pathway. Eight of 29 patients who expressed phospho-S6 died, whereas all 9 patients lacking p-S6 expression were alive at last follow-up. There was an inverse relationship between expression of phospho-S6 and survival (p=0.029). There were trends towards decreased survival in patients expressing phospho-PRAS40 (p=0.077) and those exhibiting PTEN promoter methylation (p=0.128). Thus, survival of LGG patients correlates with activation of the PI3K pathway, as reflected in phosphorylation of the downstream molecules (McBride 2010).

As prospective molecular data are lacking, this study is a perfect cohort in which to prospectively assess the frequency of PI3K activation in LGGs, evaluate the mechanism of such activation, and confirm that aberrant signaling predicts for poor survival. Translational studies as well the exploratory progression endpoints will help clinicians decide if future patients should be treated at the time of first radiographic progression or if another endpoint is
more important in predicting patients at risk for early symptomatic tumor progression despite the “low-risk” nature of this subset of LGG patients.

Mutations in metabolic enzymes have recently emerged as common genetic aberrations in astrocytomas and oligodendrogliomas. Mutations in the NADP\(^+\)-dependent isocitrate dehydrogenases 1 and 2 (\textit{IDH1} and \textit{IDH2}) occur frequently in some types of World Health Organization grades 2 to 4 gliomas and are specific to codons that encode conserved functionally important arginines in the active site of each enzyme. Published studies report that \textit{IDH1} mutations occur at the Arg132 codon whereas mutations in \textit{IDH2} have been identified at the Arg140 codon, as well as at Arg172, which is aligned with \textit{IDH1} Arg132. \textit{IDH1} and \textit{IDH2} mutations are usually heterozygous in gliomas. Mutation frequencies of \textit{IDH1} Arg132 in grade 2 gliomas, grade 3 gliomas, and secondary glioblastoma vary from 50% to 94% in various studies, but occur less frequently in primary glioblastomas and other cancers.

10.4.2 Molecular Studies

10.4.2.1 Whole Transcriptome Analysis

Whole transcriptome analysis will be performed on RTOG 0925 cases. This will include analysis of expression of all coding and noncoding RNAs, single nucleotide polymorphisms (SNPs), mutations, chromosomal aberrations, and identification of alternative splicing variants. These analyses will also establish the 1p/19q deletion status of each tumor.

10.4.2.2 Immunohistochemical Assays

All antigens to be assayed in this protocol are cytoplasmic or membranous and will be scored using a semi-quantitative scale as described previously:

To examine whether the \textit{PTEN} promoter is methylated in glioma specimens, we will use methylation-specific primers that had previously been used to demonstrate methylation of the \textit{PTEN} promoter in a subset of non–small cell lung cancer samples. These primers amplify a 181 base pair region of the \textit{PTEN} promoter that starts 2477 nucleotides from the translation start site. The methylation-specific PCR (MSP) assay is sensitive to approximately 5% methylated product.

10.4.2.3 Summary of Assays To Evaluate PI3K/Akt Pathway and IDH1 Mutations

<table>
<thead>
<tr>
<th>Molecular feature</th>
<th>Assay (reagents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorylated P70(^{S6K})</td>
<td>IHC: Abcam #AB32359 (Mouse)</td>
</tr>
<tr>
<td>\textit{PTEN} expression</td>
<td>IHC: Cell Signaling #9559 (Rabbit)</td>
</tr>
<tr>
<td>Phosphorylated S6 235/236</td>
<td>IHC: Cell Signaling #2211 (Rabbit)</td>
</tr>
<tr>
<td>Phosphorylated S6 240/244</td>
<td>IHC: Cell Signaling #2215 (Rabbit)</td>
</tr>
<tr>
<td>Phosphorylated PRAS40 (pT246)</td>
<td>IHC: Cell Signaling #2997 (Rabbit)</td>
</tr>
<tr>
<td>Phosphorylated 4EBP1</td>
<td>IHC: Cell Signaling #2855 (Rabbit)</td>
</tr>
<tr>
<td>\textit{IDH1} mutations (\textit{IDH1}R132H)</td>
<td>IHC: Dianova #DIA H09 (Mouse)</td>
</tr>
<tr>
<td>\textit{PTEN} promoter methylation</td>
<td>Methylation-specific primers as described</td>
</tr>
</tbody>
</table>

In addition to the above, levels of pAKT, pmTor, pMAPK, PDGFR1, IGFR1, NFkB, Ki-67, and Src will be assessed. Protein expression levels will be assessed using the Histo-Rx AQUA platform.

10.4.2.4 Global Methylation

The MethylMiner Methylated DNA Enrichment Kit will be used for the enrichment and fractionation of methylated double-stranded DNA (dsDNA) based on the degree of methylation. In this kit, methylated DNA is isolated from fragmented whole genomic DNA (5 ng–25 μg) via binding to the methyl-CpG binding domain of human MBD2 protein, which is coupled to paramagnetic Dynabeads M-280 Streptavidin via a biotin linker. The methylated fragments can then be eluted as a single enriched population with a 2000 mM NaCl elution buffer or into distinct subpopulations based on the degree of methylation by increasing the NaCl concentration of the elution buffer from 200 mM to 2000 mM in a
stepwise gradient. The downstream application will then be either direct sequencing or library preparation for high-throughput sequencing assays.

10.4.2.5  
**Micro or Non-Coding RNA**  
Micro RNAs or noncoding RNAs are involved in a variety of cellular processes including complex regulatory functions. They are single-stranded RNAs that are typically 19 to 22 nucleotides long and believed to regulate gene expression post-transcriptionally by binding to the 3'-UTR and inhibiting translation. Isolated micro-RNA will be probed for its differential regulation across the tissue samples using applied Biosystem TILDA cards. Comprehensive coverage of Sanger miRBase v14 is enabled across a 2-card set of TaqMan® Array MicroRNA Cards (Cards A and B) for a total of 754 unique assays specific to human miRNAs. In addition, each card contains 4 control assays—3 carefully selected candidate endogenous control assays and negative control assay. Card A focuses on more highly characterized miRNAs, while Card B contains many of the more recently discovered miRNAs along with the miR* sequences.

10.4.2.6  
**Data Analysis**  
We will use the Ohio Supercomputer Centre’s computers to analyze the mined data. The analysis will be conducted in collaboration with the Arthur G. James Cancer Hospital of The Ohio State University Comprehensive Cancer Center. We will also use commercially available packages such as Partek Genomics Suite, Rosetta resolver, Gene Pattern Server, and Ingenuity Pathway Analysis.

Likewise, no prospective data exist on molecular correlates of NCF, QOL, or seizure frequency or control in this particular group of good-prognosis patients. Additionally, because tissue > 1 cm³ is requested on this study, we anticipate having a good amount of tissue to conduct later studies of molecular markers and their correlation to radiological presentation, NCF, QOL, and seizure frequency and control.

10.4.2.7  
**Contact Information**  
Questions concerning molecular marker analysis can be directed to:  
Joanna Phillips, MD, PhD  
Assistant Professor  
Department of Neurological Surgery and Pathology  
The Helen Diller Family Cancer Research Building  
1450 3rd Street, Room HD281, Box 0520  
San Francisco, CA 94158-9001281  
joanna.phillips@ucsf.edu/415-476-4758

10.5  
**Reimbursement**  
RTOG will reimburse institutions for submission of protocol-specified biospecimen materials sent to the RTOG Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement & Case Credit Schedule found on the RTOG Web site (http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323). Biospecimen payments will be processed quarterly and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.6  
**Confidentiality/Storage**  

10.6.1  
Upon receipt, the specimen is labeled with the RTOG protocol number and the patient’s case number only. The RTOG Biospecimen Resource 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 II.

11.2 Neurocognitive Evaluation
11.2.1 How To Get Started With CogState
11.2.1.2 Step 1: Obtaining Certification
Become certified for administering the neurocognitive tests used in RTOG 0925.

11.2.1.3 Step 2: Obtaining CogState Software
Contact RTOG Headquarters at 0925cogstate@acr.org to obtain a USB Drive.

11.2.1.4 Step 3: Administering CogState Assessments
Refer to the RTOG 0925 Neurocognitive Tests: Information for Test Administrators manual, available on the USB Drive and on the RTOG website in the miscellaneous column next to the protocol-specific materials.

See Appendices IV and V for full pre-registration examiner certification requirements.

11.2.2 CogState Test Battery
The 4 tests involve pseudo-randomization of content to provide multiple alternate forms of the tests. There are nearly unlimited alternate test forms available for 3 of the tests, and the fourth contains 20 matched alternate forms. All tests are preceded by practice items. The total time of administration is about 22 minutes.

11.2.2.1 One Card Learning Test (OCLT) (visuoperceptual learning and memory)
Standard playing cards appear in the center of the computer’s screen one at a time, and the subject presses one mouse button if the card was presented previously and the other mouse button if it was not. Eighty-eight items are presented, in 8 trials of 11 cards. Learning and memory are operationally defined as the ability to discriminate between previously presented and novel (ie, distractors) information. Recognition paradigms are especially useful for assessing encoding and storage of newly learned information (Delis 2000).

11.2.2.2 Detection Test (DET) (sensory registration, vigilance, and reaction time)
A playing card appears in the center of the screen and turns face-up every 1 to 2 seconds. The subject presses one mouse button as quickly as possible after the card turns face-up. There are 35 items.

11.2.2.3 Identification Test (IDN) (basic information processing/decision speed)
A playing card appears in the center of the screen and turns face-up every 1 to 2 seconds; the subject pushes one mouse button if the card is red and the other mouse button if it is black. There are 30 items.

11.2.2.4 Groton Maze Learning Test (GMLT) (spatial learning and executive functioning, including working memory, error monitoring, and ability to integrate feedback to modify problem solving)
Subjects must learn a hidden pathway within a grid of tiles. Each time they click on a tile (using the mouse), they receive correct/incorrect feedback to help guide them through the pathway. Subjects must apply a set of simple rules to minimize errors. There are 28 steps and 11 turns to complete the maze. There are 5 trials of the same hidden pathway.

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Test</th>
<th>Administration Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory registration, vigilance, and reaction time</td>
<td>DET</td>
<td>3</td>
</tr>
<tr>
<td>Information processing/decision speed</td>
<td>IDN</td>
<td>3</td>
</tr>
<tr>
<td>Learning and memory</td>
<td>OCL</td>
<td>8</td>
</tr>
<tr>
<td>Spatial learning and executive functioning, including working memory, error monitoring, and ability to integrate feedback to modify problem solving</td>
<td>GMLT</td>
<td>8</td>
</tr>
</tbody>
</table>
11.3 Quality of Life Evaluation: Required

Completion of the quality of life measurements [EORTC Quality of Life Questionnaire-Core 30 (QOL-30), the Brain Cancer Module-20 (BCM20), and the EQ-5D] is mandatory for this protocol. Institutions must administer the baseline and follow-up assessments for the QOL-30, the BCM20, and the EQ-5D.

11.3.1 EORTC Quality of Life Questionnaire-Core 30 (QOL-30) and Brain Cancer Module-20 (BCM20)
The EORTC QOL-C30 and BCM20 were developed and validated for use in this patient population. The QLQ-C30 is a 30-item self-report questionnaire that asks the patients to rate items on a 4-point scale, with 1 “not at all” to 4 “very much.” The instrument measures several domains, including physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, fatigue, pain, nausea and vomiting, and several single items (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial impact). The BCM20 consists of 4 scales comprised multiple items (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single items (headache, seizures, drowsiness, hair loss, itching, difficulty with bladder control, and weakness of both legs). The combined instrument takes an average of 8 minutes to complete by patients with primary brain tumors (Osoba 1998).

11.3.2 EQ-5D
The EQ-5D is a 2-part, patient self-administered questionnaire that takes approximately 5 minutes to complete (Schulz 2002). The first part consists of 5 items covering 5 dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 243 health states to which unconsciousness and death are added (Badia 1998). The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20-cm 10-point interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale, and best imaginable health state is scored as 100 at the top. Both the 5-item index score and the VAS score are transformed into a utility score between 0 “Worst health state” and 1 “Best health state.” The index score or the VAS score can be used in the quality adjusted survival analysis depending on the health state(s) of interest (Wu 2002). For this study, we will plan to report both the multidimensional and the VAS utilities for comparative purposes between standardized HRQOL and current health state but will only use the multidimensional utilities for the assessment of QALYs. The EQ-5D has now been translated into most major languages, with the EuroQol Group closely monitoring the translation process; translations can be accessed at http://www.euroqol.com.

11.3.3 Study Research Assistants (RAs) will administer the EORTC QOL-30 and BCM-20 along with the EQ-5D. The RAs will have been trained in the use of these instruments through special RTOG workshops (June 2011) and through use in previous RTOG brain studies including 0525 and 0825. As part of training and previous experience RAs will be able to answer patient questions and check for missing data.

11.3.4 The study site will monitor the patient for emotional distress and refer the patient to an appropriate behavioral health service as needed.

11.4 Measurement of Response
Currently there are no uniformly accepted radiological criteria for defining disease progression or GTR in patients with diffusely infiltrating LGG. In 1990, Macdonald et al (1990) proposed the universally accepted radiological criteria for defining disease progression in patients with enhancing malignant grade III and grade IV gliomas. As such, the Macdonald criteria do not apply to patients with non-enhancing LGGs. There is an ongoing work in progress by an international working group to define GTR and radiological progression in non-enhancing LGGs (van den Bent 2009). In this study a modification of the Macdonald criteria will be used to define radiologic progression. Determination of radiographic progression will be made by the local institution. However, MRIs will be reviewed centrally by study investigators (Drs. Choucair, Laack, and Jensen) retrospectively to confirm institutional interpretation. In addition, clinical and neurologic progression, as defined in Section 2.2.9 will be correlated with radiographic findings. All serial MRIs performed as required by the study will be submitted for central review and will be used for these analyses.
- **Measurable disease** - the presence of at least one measurable lesion; if the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter $\geq$ 10 mm using with brain MRI
- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter < 10 mm with MRI)

**Response Criteria: Evaluation of target lesions**

*Complete Response (CR):* Disappearance of all target lesions

*Partial Response (PR):* At least a 50% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD

*Progressive Disease (PD):* At least a 25% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

*Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

11.5 **Instructions for Medication/Seizure Diary**

Begin the Seizure/Medication diary at Step 2 registration. Give the patient enough forms to complete the diaries monthly and have the patient return the diaries at each clinic visit.

12.0 **DATA COLLECTION**

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

*If a data form is available for web entry, it must be submitted electronically.

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 **Summary of Data Submission** ([12/3/12])

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology Screening Form (P4)</td>
<td>Within 12 weeks prior to Step 2 registration</td>
</tr>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of Step 2 registration</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>EORTC Quality of Life Questionnaire-Core 30 (QOL-30-BN20) [QL]</td>
<td>12M, 24M, 36M, 48M, and 60M from Step 2 registration and at time of radiological progression</td>
</tr>
<tr>
<td>EQ-5D (QF)</td>
<td>12M, 24M, 36M, 42M, 48M, 54M, and 60M from Step 2 registration and at time of radiological progression</td>
</tr>
<tr>
<td>CogState Database (NP)</td>
<td></td>
</tr>
<tr>
<td>EORTC Quality of Life Questionnaire-Core 30 (QOL-30-BN20) [QL]</td>
<td></td>
</tr>
<tr>
<td>EQ-5D (QF)</td>
<td></td>
</tr>
<tr>
<td>CogState Database (NP)</td>
<td></td>
</tr>
<tr>
<td>Seizure Diary (DP)</td>
<td>Every 6 months for 6 years. Note: Patients are to complete Appendix VII. Please keep for source documentation. DO NOT submit these forms to Headquarters.</td>
</tr>
</tbody>
</table>
Follow-up Form (F1) 12M, 24M, 36M, 48M, and 60M from Step 2 registration and at time of radiological progression

Post-op MRI scan & Report (MR, ME) Within 2 weeks of Step 2 Registration

Follow-up MRI Scans & Reports (MR, ME) 12M, 24M, 36M, 48M, and 60M from Step 2 registration and at time of radiological failure, clinical failure, or neurological failure

Radiology Review Form (SR) 12M, 24M, 36M, 48M, and 60M from Step 2 registration and at time of radiological failure, clinical failure, or neurological failure

Methods of Scan Submission
RTOG can provide software (TRIAD) for installation on a PC at your site that collects, anonymizes and submits image sets from your MRI system or from your PACS. The images are “DICOM pushed” either from the MRI system or from the PACS to the PC on which the software is installed. This software anonymizes and encrypts images as they are transferred via FTP to the RTOG image archive. For more information, see https://triad.acr.org.

TRIAD Image Submission Software PC Requirements
1. Network capability to transmit data from a scanner to a linked workstation, PC, or PACS
2. A Windows XP PC available to transmit data (patient data, MR and PET image data) to RTOG:
   a. Operating System Windows XP Pro
   b. Access to the Internet: Internet Explorer
   c. Minimum of 50 GB available hard drive
   d. At least 1 GB RAM
   e. Ability to view PDF documents
3. Software utilities required:
   a. Windows Installer 3.1
   b. Microsoft .NET framework 2.0
   c. MDAC Type 2.8
   d. MS SQL 2005 Express

Please contact the TRIAD help desk (Triad-Support@acr.org) or 215-940-8820 regarding installation requirements and to arrange the installation of TRIAD software prior to first accrual.

For questions regarding image submission, call 215-574-3219.

Scans also can be submitted on CD and mailed to RTOG Headquarters.

13.0 STATISTICAL CONSIDERATIONS
13.1 Study Endpoints (8/15/13)
13.1.1 Primary Endpoint
NCF as measured by each of the 4 neurocognitive tests at baseline and periodically (12M, 24M, 36M, 42M, 48M, 54M, and 60M from Step 2 registration) for a total of 5 years, including at the time of radiological progression if applicable.

13.1.2 Secondary Endpoints
13.1.2.1 Time to neurocognitive decline, as defined by the RCI-WSD
13.1.2.2 PFS, defined as the interval from registration to progression or death, whichever occurs first. Progression here denotes radiological progression.
13.1.2.3 Association of cognitive function and radiological progression
13.1.2.4 Effect of salvage therapy on cognitive outcomes in patients who progress
13.1.2.5 QOL as measured by the EORTC QLQ-C30 and brain module EORTC QLQ-BCN20 and health utilities as measured by the EQ-5D
13.1.2.6 Frequency of seizures
13.1.2.7 Molecular correlates of QOL, NCF, seizure control, and PFS
13.1.2.8 Overall survival, defined as the interval from registration to death due to any cause
13.1.2.9 Association between change in cognitive function and symptomatic progression or clinical progression

13.2 Sample Size (8/15/13)
The objective of this observational trial includes using longitudinal data analysis to describe the trend in neurocognitive decline on each of the tests in the battery, specifically as it relates to disease progression. The sample size calculations will be based on one of the associations that will be tested: the average changes of NCF score from baseline to the time of radiological tumor progression or up to 5 years (whichever occurs first) between patients who do and do not experience radiological progression. There are currently no data available for this patient population to hypothesize expected decline(s) in NCF. Thus, an effect size of 0.50 was chosen by the investigators to represent a clinically meaningful difference to provide evidence for further evaluating NCF in this patient population (Cohen 1988). The effect size (ES) is the difference in means divided by the standard deviation. The null hypothesis is that there will be no clinically meaningful difference in the mean NCF change score, from baseline to the time of radiological tumor progression or up to 5 years (whichever occurs first) between radiologically progressed and non-progressed patients. The alternative hypothesis is that there will be a clinically meaningful difference by an effect size of 0.5 between these 2 patient groups.

\[ H_0: \Delta \mu_P = \Delta \mu_{NP} \text{ vs } H_a: \Delta \mu_P \neq \Delta \mu_{NP} \]

Based on PFS data from RTOG 9802, multiple prospective studies (Shaw 2002, van den Bent 2005; Pignatti 2002) and multiple retrospective series (Schomas 2009; Chang 2008), patient eligibility was determined such that we project that 50% of patients will have progressed within 5 years. Based on the 2-sample t-test, a total of 128 patients will ensure at least 80% statistical power to detect an effect size of 0.50 at a 2-sided significance level of 0.05. It is expected that 10% of enrolled patients will be found ineligible subsequently. Due to the long span of 5 years’ follow-up with NCF assessments, missing assessments to a certain extent are also expected. Even in the very ill, terminal patient populations, compliance with cognitive testing exceeds 80% to 90% (Regine 2004; Meyers 2004), albeit generally for shorter periods of time. Previous studies have shown excellent compliance with neurocognitive testing even with long-term follow-up in this generally healthy population (Laack 2005; Choucair, personal communication). In the study by Laack et al, low-grade glioma patients underwent 4 hours of cognitive testing at 10-month intervals. Although nearly 50% did not complete follow-up at 5 years, these patients were high risk and nearly all had progressed even after radiotherapy. We expect better participation in patients because of the shortened test schedule as well as improved performance status of this cohort. Therefore, we expect only a 15% patient attrition due to testing fatigue, loss to follow-up, or other reasons. Thus, the target sample size will be 170 supratentorial low-risk grade II glioma patients to ensure that we have 128 analyzable patients for the statistical analysis.

13.3 Patient Accrual
Based on the experience of the phase II arm of RTOG 9802 (low-risk LGG patients, observation arm) in which accrual vastly exceeded expectations, we expect improved participation in this trial. RTOG 9802 had limited eligibility to patients < 40 with neurosurgeon-defined GTR. It accrued 116 patients, averaging 2.6 patients per month. Since 9802, RTOG has become more multidisciplinary and CNS studies in general continue to exceed accrual expectations. In this trial, eligibility is more inclusive; thus expected accrual for the proposed trial is 5 patients per month and expected duration is 37 months, assuming no accrual in the first 3 months while sites obtain IRB approval. Accrual will be monitored semi-annually by the RTOG Data Safety and Monitoring Board (DSMB). If the average monthly accrual rate between 12 and 18 months is below 2 cases per month, the study will be re-evaluated for its feasibility. If the total accrual at 18
months is < 20% of the target accrual (ie, less than 15 patients have been accrued at 18 months) or the average monthly accrual between 19 and 24 months remains less than 2 patients per month, the study statistician will recommend to the RTOG DSMB that the study be terminated.

13.4 Analysis Plan

13.4.1 Primary Endpoint

The primary endpoint of NCF is measured by a battery of tests: the Detection Test (DET), the Identification Test (IDN), the One Card Learning Test (OCLT), and the Groton Maze Learning Test (GMLT). The primary outcome measure of the DET and IDN tests is speed of performance using the mean of the log10 transformed response times for correct responses (lower score = better performance). Accuracy of performance is the primary outcome measure for the OCLT, using the arcsine transformation of the square root of the proportion of correct responses across 8 rounds (higher score = better performance). Number of errors is the primary outcome measure for GMLT. NCF is comprised of 4 tests corresponding to different neurocognitive functions that are correlated ($\rho \leq 0.50$). Each of the battery’s tests will be evaluated using the 2-sample t-test with a 2-sided significance level of 0.05 to determine if there is a clinically meaningful difference in the average change of NCF score from baseline to the time of radiologic tumor progression or up to 5 years (whichever occurs first) between radiologically progressed and non-progressed patients. In order to adjust for multiple comparisons and maintain the overall type I error of 0.05, Hochberg’s procedure will be applied (Hochberg 1988).

In addition to the evaluation of NCF at the time of radiologic tumor progression or up to 5 years (whichever occurs first), overall trends in NCF will be evaluated using the general linear mixed-effects model in which disease progression, tumor histology, further treatment received if recurrence is discovered, age, education, use of anticonvulsant and psychotropic medications, and other prognostic factors that are covariates of interest. Whether the pattern of cognitive function changes over time is the same for patients receiving further treatment or not after radiological progression will also be evaluated through a general linear mixed-effects model. The available molecular marker information will also be included as a covariate to evaluate the molecular correlates of NCF.

Although no consensus exists for the definition of progression in this patient population, “radiological progression” will be used for the primary endpoint. As previously stated, there are no uniformly accepted radiological criteria for defining disease progression or GTR in patients with diffusely infiltrating LGG. Macdonald et al (1990) proposed the universally accepted radiological criteria for defining disease progression in patients with enhancing malignant grade III and grade IV gliomas. As such, the Macdonald criteria do not apply to patients with non-enhancing LGGs. There is ongoing work in progress by an international working group to define GTR and radiological progression in non-enhancing LGGs (van den Bent 2009). In this study, a modification of the Macdonald criteria will be used to define radiologic progression. An increase in size of the T2/FLAIR abnormality of 25% over baseline (or postoperative) T2/FLAIR weighted signal measurement should be considered as evidence for radiological progression, provided there is no other explainable cause for the increased T2/FLAIR signal (eg, recent seizures, trauma, a cerebrovascular event, metabolic causes or other etiologies).

Participation in the scheduled NCF assessment is mandatory in this study. Adherence to the component assessment schedule will be encouraged through phone call reminders to participating institutions. Completion of all scheduled assessments is part of the routine delinquency assessment for participating institutions. Because it is unlikely that patient assessments will occur exactly as scheduled, the statistical analysis will allow an acceptable window of ± 1 month (2 month timeframe) at each assessment time. The RTOG Statistics and Data Management Center staff will monitor proportions of missing NCF information at different assessment points. In spite of efforts made to increase compliance, missing data are expected. Cases with missing data will be reviewed to determine their potential impact on the data set as a whole, including progression status. Mean scores on the primary items will be compared for patients with and without missing data at different assessment points to identify whether
missing data was preceded by a significant decline in neurocognitive test scores. Mean scores by assessment time for cohorts stratified by baseline score quartile will also be compared to investigate whether the missing data are random or show a pattern that might bias analytic findings. If the missing data appear random, analyses will include imputation for the missing values. Possible methods of imputation for missing values may include use of variable means of completed cases, use of mean values of other variables, or a combination of these methods. If the missing data form a non-randomized pattern, depending on severity, we will use appropriate analytic strategies to control for potential bias and, where possible, impute missing data. Imputation methods for non-random scenarios may include use of the means for individuals who withdraw from the trial from either all or similar (matched) subjects remaining in the trial, last observation carried forward, or a combination of these methods. Sensitivity analyses based on the varying assumptions about the missing data mechanisms will also be conducted.

13.4.2 Interim Review of Data Compliance
Efforts will be made to target optimal data collection. This will require help from research assistants (RAs) at participating institutions. The primary endpoint requires at least the following neurocognitive assessments: baseline and at the time of radiological progression or at 5 years (whichever occurs first). To ensure high data quality, baseline compliance for the neurocognitive battery will be reviewed semi-annually. Target baseline compliance is at least 95%. If baseline compliance is 85% to 95%, the trial will be re-evaluated for feasibility. If baseline compliance is < 85%, the trial will terminate. Percentages will be based on the number of patients completing the baseline assessment out of the total number of eligible patients accrued.

Follow-up compliance for the neurocognitive battery will be reviewed annually. Patients may intermittently miss a scheduled follow-up neurocognitive assessment. If the baseline assessment is completed, patients with occasional missing assessments will still be used in the statistical analysis. At each annual review, patients will have differing potential follow-up times. Analyzable patients at each time point are patients who have completed the baseline assessment and have been in the study potentially longer than the scheduled time point (adjusting for a 3-month grace period for data submission). The compliance rate for follow-up at a scheduled time point will be calculated. For each rate, the denominator will be the number of analyzable patients and the numerator is the number of analyzable patients with neurocognitive data for that time point. The following table lists the evaluation rules for the NCF data collection.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Trial terminated</th>
<th>Trial re-evaluated for feasibility</th>
<th>Target compliance met</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Progressors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 Follow-Up</td>
<td>&lt; 85%</td>
<td>85% - 95%</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>Year 1</td>
<td>&lt; 80%</td>
<td>80% - 90%</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>Year 2</td>
<td>&lt; 80%</td>
<td>80% - 90%</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>Year 3</td>
<td>&lt; 80%</td>
<td>80% - 90%</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>Year 4</td>
<td>&lt; 80%</td>
<td>80% - 90%</td>
<td>≥ 90%</td>
</tr>
<tr>
<td>Year 5</td>
<td>&lt; 80%</td>
<td>80% - 90%</td>
<td>≥ 90%</td>
</tr>
<tr>
<td><strong>Progressors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of Progression</td>
<td>&lt; 85%</td>
<td>85% - 95%</td>
<td>≥ 95%</td>
</tr>
</tbody>
</table>

* Given that patients may intermittently miss assessments, analyzable patients at each follow-up assessment are patients who have completed the baseline assessment and have been in the study longer than the specific time point

Given a target accrual of 170 and assuming a 10% clinically ineligible rate, the above criteria will yield an analyzable sample size of at least 134, which meets the target analyzable size of 128.
<table>
<thead>
<tr>
<th>Total Eligible Accrual</th>
<th>Assessment</th>
<th>Percentage (number) of Analyzable Patients Completing Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=153</td>
<td>Baseline</td>
<td>Trial terminated &lt; 85% (n ≤ 129)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trial re-evaluated for feasibility 85% - 95% (130 ≤ n ≤ 144)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Target compliance met ≥ 95% (n ≥ 145)</td>
</tr>
</tbody>
</table>

Non-Progressors (N=72)

- At least 1 year Follow-Up: < 85% (n ≤ 60)
- Year 1: < 80% (n ≤ 57)
- Year 2: < 80% (n ≤ 57)
- Year 3: < 80% (n ≤ 57)
- Year 4: < 80% (n ≤ 57)
- Year 5: < 80% (n ≤ 57)

Progressors (N=73)

- Time of Progression: < 85% (n ≤ 61)
- 85% - 95% (61 ≤ n ≤ 69)
- ≥ 95% (n ≥ 69)

* Given that patients may intermittently miss assessments, analyzable patients at each follow-up assessment are patients who have completed the baseline assessment and have been in the study longer than the specific time point.

13.4.3 Secondary Endpoints

13.4.3.1 Time to Neurocognitive Decline

Time to neurocognitive decline will be evaluated in patients who progress and do not progress radiologically. The cumulative incidence approach will be used to estimate the median time to neurocognitive impairment to account for the competing risk of death and to determine if there is a clinically meaningful difference in the time to neurocognitive decline, as defined by the RCI-WSD (reliable change index—within-subjects standard deviation), between radiologically progressed and non-progressed patients.

Methods of detecting change have evolved over time (Collie 2002). A version of a RCI (Lewis 2007) will be used to determine whether each subject’s follow-up scores show a change from baseline. Use of RCIs provides statistical decision rules to differentiate change and stability; of the 4 in common use, RCI-WSD was selected to account for associated error including practice effects resulting from repeated administration of tests. The WSD is drawn from a control group (cogstate.com normative values) and may be used to reflect measured individual variability (Bland 1996). For each neurocognitive test, if the score difference between baseline and each follow-up exceeds the RCI-WSD for that test, it is defined as neurocognitive decline. However, to guard against Type I error, decline for a given subject is defined as decline on at least 2 of the 4 tests (Lewis 2006; Silbert 2004; Rasmussen 2001).

The NCF change (decline versus no decline) from baseline to each follow-up assessment is a time-dependent covariate. To determine if the NCF decline is an earlier warning biomarker to radiologic progression, we will use NCF change as a time-dependent covariate in a Cox proportional hazards (PH) regression model with radiological progression as the endpoint. All eligible patients in this study (both radiologically progressed and non-progressed patients) will be included in this analysis. The Cox model estimates the ratio of hazard rate of radiographic failure with and without neurocognitive decline. Anticonvulsant use, tumor size, tumor histology, and further treatment received if recurrence is discovered, which may also have impact on the radiological progression, will also be considered in this Cox PH regression analysis to assess the effects of these covariates on the hazard rate of radiographic failure. Therefore, both time-dependent factor (neurocognitive function change) and fixed-time factors (anticonvulsant use, tumor size, etc) should be included in the Cox PH model. The relationship between the time-dependent factor and fixed factors will also be examined through an additional set of time-dependent covariates that represent interactions between the timing of NCF decline and the fixed-time covariates. To determine which of the time-dependent interaction factors should be included in the final model, a forward, stepwise selection procedure is used through the likelihood ratio tests.
13.4.3.2 **Quality of Life**

Participation in the scheduled quality of life assessments is mandatory in this study. QOL will be evaluated using the EORTC QLQ-C30 with the BN-20 module. The QLQ-C30 is composed of both multi-item scales and single-item measures including 5 functional scales, 3 symptom scales, a global health status/QOL scale, and 6 single items. Each of the multi-item scales includes a different set of items; no item occurs in more than one scale. All of the scales and single-item measures range in score from 0 to 100. A high score represents a higher response level. Thus, a high score for a function scale represents a high/healthy level of functioning; a high score for the global health status/QOL represents a high QOL (i.e., a better state of the patient). Conversely, a high score for a symptom scale on the BN-20 item represents a high level of symptomatology/problems (i.e., worse state of the patient). The QLQ-C30 and its modules have been designed to evaluate change of HRQOL in a clinical trial setting. As such, a single individual score is not considered to be informative. Scores are only informative when used in a comparative setting such as comparing changes within the LGG group over time. For the EORTC QLQ-C30 and BN-20, a change in any scale of at least 10 points is considered to be clinically relevant (Osoba 1998).

Health utilities will be evaluated using the EQ-5D. The utility scores lie between 0 “Worst health state” and 1 “Best health state.” It will provide 2 utility scores: 1 from the 5-item index score and the other from the visual analogue scale (VAS), and both will be used in generating separate quality-adjusted survivals. Quality-adjusted survival will be computed using the weighted sum of different time in different health states added up to a total quality-adjusted survival time where $U = \sum q_i s_i$. The general linear mixed-effects model will be used to evaluate the changes of QOL and health utilities over time. The available molecular marker information will also be included as a covariate to evaluate the molecular correlates of QOL.

Missing data for QOL assessments are expected and will be handled in a similar manner as done for the primary endpoint, NCF.

13.4.3.3 **Seizure Frequency**

Seizure frequency will be evaluated using a patient seizure diary. A change in seizure frequency of > 50% is considered significant. This is the definition of significant change that is currently in usage in epilepsy clinical trials. Marginal models will be used to evaluate the change of frequencies of seizures over time for up to 5 years. Anticonvulsant use, tumor size, tumor histology, further treatment received if recurrence is discovered, and other prognostic factors will also be included in the covariates sets. The available molecular marker information will also be included as a covariate to evaluate the molecular correlates of seizure frequency.

13.4.3.4 **PFS and Overall Survival (OS)**

PFS and OS rates will be estimated using the Kaplan-Meier method, and difference between the activation of different signaling pathways will be tested using the log rank test. Multivariate analyses with the Cox proportional hazards model for OS and PFS will be performed to assess the activation of the signaling pathway effect adjusting for patient-specific risk factors. The covariates to be evaluated for the multivariate models are: activation of signaling pathway status, age, tumor size, and other prognostic factors.

To explore the relationship between change in cognitive function and symptomatic progression or clinical progression (defined as initiation of treatment interventions such as radiotherapy, chemotherapy, or additional surgery), we will use NCF change as a time-dependent covariate in a Cox PH regression model with the symptomatic progression and/or clinical progression as the endpoint. The NCF function change (decline versus no decline) from baseline to each follow-up assessment is a time-dependent covariate. The effect of anticonvulsant use, tumor size, tumor histology, and other prognostic factor will also be adjusted.

13.4.3.5 **Definition of Progression**

Because no consensus exists for the definition of progression in these patients, 2 additional definitions of progression will be explored for the correlation with cognitive changes and QOL in addition to “radiological progression” as described for the primary endpoint.
Because this radiographic definition defines progression after fairly minimal growth, it is expected in this study that radiographic progression may not lead to therapeutic intervention.

Additionally, "symptomatic progression" will be recorded. Development of new or progressive neurologic symptoms and new or increased seizure frequency are used more often than radiologic changes to determine progression and initiate further therapy and will be explored in this study.

Finally, “clinical progression” will also be defined by initiation of further therapy (ie, additional surgery, chemotherapy, or radiation).

13.5 Interim Reports to Monitor Study Progress (8/15/13)
Interim reports will be prepared semi-annually until the primary efficacy analysis has been accepted for presentation or publication. These reports will contain the following, at a minimum: patient accrual rate and projected completion date for the accrual phase; total institution accrual; patient exclusions and reasons for exclusion; pretreatment characteristics for eligible patients; and patient compliance with baseline QOL assessments. The interim reports will not contain treatment results with respect to the primary or secondary endpoints.

13.6 Reporting the Initial Treatment Results
The primary hypothesis of this study is to describe the trend in neurocognitive decline on each of the tests in the battery, specifically as it relates to disease progression. This final analysis will occur after 128 evaluable patients have been potentially followed for 5 years. It will include tabulation of all cases entered and those excluded from the analyses with the reasons for such given; the distribution of the important prognostic baseline variables; and observed results with respect to the primary and secondary endpoints. The primary hypothesis will be evaluated using the 2-sample t-test as specified in the analysis plan. Also, where feasible, treatment evaluation with respect to all endpoints will be compared within each racial and ethnic category.

13.7 Gender and Minorities
In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, participation rates of women and minorities will be examined during the interim reports. Based on accrual statistics from RTOG 9802, the projected accrual by gender, race, and ethnicity is shown below:

Projected Distribution of Gender and Minorities

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>8</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>77</td>
<td>77</td>
<td>154</td>
</tr>
<tr>
<td>Ethnic Category: Total</td>
<td>85</td>
<td>85</td>
<td>170</td>
</tr>
<tr>
<td>Racial Category</td>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td>Asian</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Black or African American</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
</tr>
<tr>
<td>White</td>
<td>77</td>
<td>77</td>
<td>154</td>
</tr>
<tr>
<td>Racial Category: Total</td>
<td>85</td>
<td>85</td>
<td>170</td>
</tr>
</tbody>
</table>
REFERENCES


APPENDIX I

Informed Consent Template for Cancer Treatment Trials  
(English Language)

RTOG 0925

NATURAL HISTORY OF POSTOPERATIVE COGNITIVE FUNCTION, QUALITY OF LIFE, AND SEIZURE CONTROL IN PATIENTS WITH SUPRATENTORIAL LOW-RISK GRADE II GLIOMA

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a slow growing brain tumor called a low grade glioma.

Why is this study being done?
The purpose of this study is to understand the effects of your brain tumor and surgery on your cognitive function (thinking abilities, memory), quality of life, and seizures.

How many people will take part in the study?
About 170 people will take part in this study.

What will happen if I take part in this research study?
Before you begin the study …
Your study doctor will need to send the block of tumor tissue obtained at the time of your brain tumor surgery to a central pathology site. There, a pathologist will confirm that the tumor is a low-grade glioma. If the tumor is not a low-grade glioma, you will not be able to continue in the study.

If the tumor is a low-grade glioma, you will need to have the following exams, tests or procedures to find out if you can continue in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical examination, including neurologic examination
- MRI of your brain

During the study …
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- History and physical examination, including neurologic examination, every 6 months
- MRI of your brain every 6 months

The study will also consist of the following:
A 20-25 minute testing session that will measure some aspects of your thinking functions, such as your memory. The testing sessions will be conducted when you enter the study and then at 12, 24, 36, 48, 54, and 60 months after you enter the study. You will also have an additional testing session before you undergo any further treatment for your tumor (re-operation, radiation, or chemotherapy).

- You will do these tasks on a computer. You do not need to be familiar with computers to complete the tasks, and you won’t have to type—you only need to press one of two buttons. The tasks are not like tests given in school; they are like games.
- The computer used for the cognitive tasks will be located in a quiet area relatively free of distractions and with reasonable lighting, comfortable seating, and a table of sufficient size for the computer.

You will be asked to complete 3 questionnaires at the following times: on your first visit; at 12, 24, 36, 48, and 60 months afterwards; and before you undergo any further treatment for your tumor (re-operation, radiation, or chemotherapy). It takes less than 15 minutes to fill out the questionnaires. The questionnaires will assess how you are feeling physically and emotionally during your cancer treatment and also how you are able to carry out your day-to-day activities. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

You will be asked to complete a seizure diary when you enter the study and every 6 months while you are on the study. The diary will assess how frequently you are having seizures.

How long will I be in the study?
You will be asked to take the testing sessions for about 4 and a half years. After you have completed these sessions, the study doctor will ask you to visit the office for follow-up exams for at least 5 years.

Can I stop being in the study?
Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop.

It is important to tell the study doctor if you are thinking about stopping, so that you and your study doctor can discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?
Your involvement in this study does not involve any physical risk to you. However, you will be asked to spend time on tasks that you would not otherwise spend time on. There is also a very small risk that your personal information may be released. Please review the section below, “Will my medical information be kept private?”.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?
You may or may not benefit from participating in this study. However, the study doctors hope that the information from this study will help researchers learn more about patients with low-grade gliomas. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?
Your other choices may include:
- Being followed for your tumor without being in a study
- Taking part in another study

Talk to your study doctor about your choices before you decide if you will take part in this study.
Will my medical information be kept private? (12/3/12)
Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:
- The Radiation Therapy Oncology Group
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Your scores from the neurocognitive test sessions will not be shared with you or your healthcare providers and are for research purposes only. If requested, you may receive a summary of this research study’s findings at the conclusion of the study. The summary will discuss general findings from the study and will not contain your name or those of other participants or a list of scores for each participant.

What are the costs of taking part in this study? (8/15/13)
You and/or your health plan/insurance company will not need to pay for the cost of administering the memory testing sessions. You and/or your health plan/insurance company will need to pay for some of the costs of the clinic visits and MRIs associated with the study in conjunction with regular care for your tumor.

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor, __________________ [investigator’s name(s)], if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at __________________ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to phase I, I/II, and II RTOG clinical trials. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at __________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at __________________ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.

You can say “yes” or “no” to each of the following studies. Below, please mark your choice for each study.

Consent Form for Use of Tissue, Blood, and Urine for Research

About Using Tissue, Blood, and Urine for Research
You have had a biopsy (or surgery) to see if you have cancer. Your doctor removed some body tissue to do some tests. The results of these tests have been given to you by your doctor and are being used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available at [http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm](http://cdp.cancer.gov/humanSpecimens/ethical_collection/patient.htm).

We would also like to collect for future research about three tablespoons of blood and three tablespoons of urine. We would collect the blood and urine before you begin the first memory testing session.

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About
The choice to let us keep your specimens for future research is up to you. No matter what you decide to do, it will not affect your care or your participation in the main part of the study.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any specimens that remain will no longer be used for research and will be returned to the institution that submitted it or destroyed.

In the future, people who do research may need to know more about your health. While the [researcher/institution] may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records. Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new treatments for cancer in the future.
**Benefits**
The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**Risks (8/15/13)**
The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included. The samples are given a code to protect your privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives.

Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

Many states have laws to protect against genetic discrimination *([list appropriate state information if your state or locality has such laws]*)*. Additionally, a federal law called the Genetic Information Non-Discrimination Act, or GINA, is in effect. This law prohibits health insurer or employer discrimination. The law does not include other types of misuse by life insurance, disability, or long term care insurance. To learn more about the GINA Law, please ask *[Note to local investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here]*.

**Making Your Choice**
Please read each sentence below and think about your choice. After reading each sentence, circle “Yes” or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at ________________ [IRB’s phone number].

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue □Yes □ No
   - Blood □Yes □ No
   - Urine □Yes □ No

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer’s disease, or heart disease), as follows:
   - Tissue □Yes □ No
   - Blood □Yes □ No
   - Urine □Yes □ No

3. Someone may contact me in the future to ask me to take part in more research.
   □Yes □ No
Where can I get more information? (12/3/12)
You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/ 

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://www.cancer.gov/cancertopics/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature
I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant ______________________________
Date ________________________________
### APPENDIX II: STUDY PARAMETER TABLE

<table>
<thead>
<tr>
<th>Pre-Registration</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 84 days prior to Step 2 registration</td>
<td>≤ 14 days of Step 2 registration</td>
</tr>
<tr>
<td>Histo/cyto eval</td>
<td>X</td>
</tr>
<tr>
<td>Tissue collection for central review</td>
<td>X</td>
</tr>
<tr>
<td>History/physical</td>
<td>X</td>
</tr>
<tr>
<td>Neurologic exam</td>
<td>X</td>
</tr>
<tr>
<td>Brain MRI w/ &amp; w/o gadolinium</td>
<td>X (70 days post surgery preferred)</td>
</tr>
<tr>
<td>Performance status</td>
<td>X</td>
</tr>
<tr>
<td>Seizure calender</td>
<td></td>
</tr>
<tr>
<td>CogState</td>
<td>X</td>
</tr>
<tr>
<td>QOL</td>
<td>X</td>
</tr>
<tr>
<td>Tissue submission for banking and translational research (for consenting patients)</td>
<td>X</td>
</tr>
<tr>
<td>Blood submission for banking and translational research (for consenting patients)</td>
<td>X</td>
</tr>
<tr>
<td>Urine submission for banking and translational research (for consenting patients)</td>
<td>X</td>
</tr>
</tbody>
</table>

*See Section 11.5 for details.*
# APPENDIX III

## KARNOFSKY PERFORMANCE SCALE

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

CERTIFICATION AND ADMINISTRATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY

EXAMINER CERTIFICATION FOR RTOG 0925

Institutions must meet certification requirements for administering neurocognitive assessments. This appendix describes the procedures in detail. Most sites should have at least two certified neurocognitive test administrators. For those small sites that do not, when scheduling appointments, every effort should be made to ensure that the certified examiner is available during the patient’s visit.

Upon review and successful completion of the Neurocognitive Certification, Dr. Caine will notify the certified administrator and CTSU that the administrator has successfully completed certification requirements.

Summary of certification procedures:
1. Test administrator candidates review 0925 neurocognitive tests instruction manual.
2. Candidates self-administer the CogState tests, as if they were a subject.
3. Candidates complete RTOG 0925 neurocognitive knowledge quiz and fax or email quiz to the Neuropsychology Co-Chair, Chip Caine, PhD.
4. Dr. Caine grades the quiz and emails candidate pass/fail feedback. The quiz is "open book," so candidates may review the manual while taking the quiz.
5. Dr. Caine will notify candidates and CTSU of certification for RTOG 0925. Test administrators are now ready to administer tests to study subjects.

Note: The CogState test software automatically adjusts each administration so that patients receive alternate forms of the tests.

TEST INSTRUCTIONS AND ADMINISTRATION PROCEDURES

Additional comments:
1. The computer used for the cognitive tests must be located in a quiet area relatively free of distractions and with reasonable lighting, comfortable seating, and a table of sufficient size for the computer. No family members or friends of the patient, or site colleagues, may be present during testing, even if they remain quiet or sit in the back of the room.
2. Testing must be completed in 1 session. Test instructions must be followed verbatim (test instruction scripts for each of the 4 tests are provided in the neurocognitive tests manual) with every patient at every study visit.
3. Tests are administered in the following order to every patient:

CogState tests instructions script

<table>
<thead>
<tr>
<th>Important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turn the computer screen so that it faces the subject. Ensure that the screen is positioned so that it is directly in front of the subject (not angled to the side) and at a comfortable distance from the subject. Adjust the screen pitch if necessary.</td>
</tr>
</tbody>
</table>
Detection Test (DET)

Before the Detection Test begins, a screen appears that allows the subject to practice entering “yes” and “no” responses via the mouse. The left mouse button is always “no” and the right mouse button is always “yes,” regardless of the hand used. Ensure that the subject understands by practicing clicking the proper buttons several times. Do not permit the subject to use the keyboard to enter responses.

Click Enter to begin the Detection test.

The instructions appear on the screen. The subject should read them silently as you read them aloud.

Say, Has the card turned over? You are now going to do a practice. You will only need to use the “Yes” button for this task. In this task, a playing card will appear in the center of the screen. Press the “Yes” button when the card turns face-up as fast as you can. If you make a mistake you will hear an error sound. This means you have responded too soon. Try to make your response as accurate and fast as possible after a card turns face-up. Are you ready to start?

Click Enter to begin the practice items. Remind the subject to press the “Yes” button as soon as the card turns face-up.

If the subject appears confused or responds incorrectly, review the test requirements, including use of the right mouse button (the “Yes” button) for responses. Ensure the subject understands that in this test, all cards shown are the same Joker card. There is no need for the subject to examine details of the card closely.

When the practice items are complete, the instructions for the scored or “real” portion of the test appear.

Say, Has the card turned over? You are now going to do the real test. Are you ready to start?

Click Enter to begin the scored items.

When presentation of items is complete, the Detection test ends and the Identification Test begins automatically.

Identification Test (IDN)

The instructions appear on the screen. The subject should read them silently as you read them aloud.

Say, Is the card red? You are now going to do a practice. You will need to use both the “Yes” and “No” buttons for this task. In this task, a playing card will appear in the center of the screen. As soon as it turns face-up you must decide: is the color of the card red? If it is red, press the “Yes” button. If it is not red, press the “No” button. If you make a mistake you will hear an error sound. Try to make your responses as accurate and fast as possible after a card turns face-up. Are you ready to start?

Click Enter to begin the practice items. Remind the subject to press the “Yes” or “No” buttons as quickly and accurately as possible.

If the subject appears confused or responds incorrectly, review the test requirements, including use of the left and right mouse button (left button = “No” and right button = “Yes” for responses. Ensure the subject understands that in this test, all cards shown are the same Joker card, the only difference being color (red or black). There is no need for the subject to examine details of the card closely.

When the practice items are complete, the instructions for the scored or “real” portion of the test appear.

Say, Is the card red? You are now going to do the real test. Are you ready to start?
Click Enter to begin the scored items.

When presentation of items is complete, the Identification test ends and the One Card Learning Test begins automatically.

One Card Learning Test (OCLT)

The instructions appear on the screen. The subject should read them silently as you read them aloud.

Say, Have you seen this card before in this task? You are now going to do a practice. You will need to use both the "Yes" and "No" buttons for this task. In this task, a playing card will appear face-down in the center of the screen and then turn face-up. As soon as a card turns face-up decide if you have seen it before in this task. Only a few of the face-up cards will repeat during the task. If you have seen the card before in this task, press the “Yes” button. If you have not seen the card before in this task, press the “No” button. If you make a mistake you will hear an error sound. Try to make your responses as accurate and fast as possible after the card turns face-up.

Click Enter to begin the practice items.

Ensure that the subject understands that now the stimuli are standard playing cards (no jokers, no tricks such as slightly altered cards) and when deciding whether the card in view was shown before, color, number, and suit must all be considered before responding. If the subject appears confused or responds incorrectly, review the test requirements, including use of the left and right mouse button (left button = “No” and right button = “Yes” for responses.

When the practice items are complete, the instructions for the scored or “real” portion of the test appear.

Say, Have you seen this card before in this task? Cards seen in the practice are not used again. You are now going to do the real test.

Click Enter to begin the scored items.

If the subject appears confused, offer a single prompt. Say, Have you seen this card before in this task?

When presentation of items is complete, OCLT ends and the Groton Maze Learning Test begins automatically.

Groton Maze Learning Test (GMLT)

Test administrators should expect to provide active assistance to subjects during the practice portions of this test, as it is somewhat complex. In brief, subjects must find a hidden pathway in a grid of tiles. The practice portion involves a small grid, presented three times, and each time the subject must try to find the same hidden pathway. The scored portion involves a larger grid, presented five times, and each time the subject must try to find the same hidden pathway within the larger grid.

Say, Find the hidden pathway. This is a practice to help you learn the rules of this maze. To begin, you must tap the top left blue tile, and then find the hidden pathway by tapping on tiles one at a time until you get to the tile in the lower right corner. The first time you try to find the pathway, you need to guess each step. A green tick means you were correct, but a red cross means the move was wrong. After a wrong move, you need to go back to the last correct tile, and then try a move in a different direction. The rules of this task are: 
1. Only move to adjacent tiles (up, down, left, or right).
2. Do not move diagonally.
3. Do not move backwards along the pathway.
4. Do not tap twice on the same tile.

Tap as quickly and accurately as you can.

Click Enter to begin the practice maze.

If the subject appears confused or responds incorrectly, review the four rules, including, if needed, that the blue tile is the starting point and that after a red cross, go back to the last correct tile (green tick), click it, and try a move in a different direction.

When the target is reached, a new grid appears (the pathway is the same, however).

Say, You must now find the same hidden pathway. To begin, tap the top left blue tile, and then tap on the hidden pathway one tile at a time until you get to the target tile. The rules are the same as before. Tap as quickly and accurately as you can.

If the subject appears confused or responds incorrectly, review the four rules, including, if needed, that the blue tile is the starting point and that after a red cross, go back to the last correct tile (green tick), click it, and try a move in a different direction. When the target is reached, a new grid appears (the pathway is the same, however). This process occurs for a total of three practice maze trials, after which the instructions appear once again.

When the instructions screen appears, say, Find the hidden pathway. You are now going to do the real test. To begin, you must tap the top left blue tile, and then find the hidden pathway by tapping on tiles one at a time until you get to the tile in the lower right corner. The first time you try to find the pathway, you need to guess each step. A green tick means you were correct, but a red cross means the move was wrong. After a wrong move, you need to go back to the last correct tile, and then try a move in a different direction. The rules of this task are:

1. Only move to adjacent tiles (up, down, left, or right).
2. Do not move diagonally.
3. Do not move backwards along the pathway.
4. Do not tap twice on the same tile.

Tap as quickly and accurately as you can.

Click Enter to begin the maze. Do not review task rules during the scored portions of the test. If, during the real test, subjects ask you to review the instructions because they forgot them or don’t know what to do, or ask you to clarify something, say, “The rules won’t let me help you.” Encourage subjects to do their best. Encourage them to guess if they aren’t sure of the correct next move.

When the target is reached, a new grid appears (the pathway is the same, however). This process occurs for a total of five scored maze trials.
Say, You must now find the same hidden pathway. To begin, tap the top left blue tile, and then tap on the hidden pathway one tile at a time until you get to the target tile. The rules are the same as before. Tap as quickly and accurately as you can.

Click Enter to begin.

When GMLT is finished, the subject receives a cheer.

The CogState tests are complete.

© 2009 CogState Limited. (The above instructions script was edited slightly for clarity.)
CERTIFICATION WORKSHEET FOR RTOG 0925 NEUROCOGNITIVE TEST ADMINISTRATORS

This worksheet must be completed and signed by each person requesting certification and must then be submitted to Dr. Caine prior to registering any patients on RTOG 0925.

____ (Y/N)  1. Have you reviewed the RTOG Study 0925 Neurocognitive Tests: Information for Test Administrators manual thoroughly?
____ (Y/N)  2. Have you self-administered each of the four tests?
____ (Y/N)  3. Have you completed the Study 0925 neurocognitive tests quiz?
____ (Y/N)  4. Have you sought satisfactory clarification of any questions you may have?
____ (Y/N)  5. Do you believe you are ready to serve as a test administrator for RTOG 0925?
____ (Y/N)  6. I have completed certification for the neurocognitive portion of RTOG 0933.

(Please Print)
Name of test administrator: __________________________

Institution number/name: __________________________

NCI code: __________________________

Telephone number of test administrator __________________________

Fax number of test administrator: __________________________

E-mail address of test administrator: __________________________

__________________________________________  _______________________
Signature of test administrator     Date

If you have questions regarding certification, please contact Chip Caine, PhD at 801-507-9835.

RTOG 0925 Test Administrator or Research Associate: Once this worksheet is complete, please attach the 0925 Neurocognitive Tests Training Quiz and send both to Dr. Caine via scan and email(to chip.caine@imail.org) or fax (801.507.9801).

Dr. Caine will e-mail the reviewed form, indicating his decision (via the box below) to CTSU, CTSURegOffice@ecogchair.org and to RTOG HQ, 0925cogstate@acr.org.

(For Dr. Caine’s Use Only)

☐ Reviewed and approved

☐ Reviewed and not approved: Dr. Caine also will contact the site

__________________________________________  _______________________
Chip Caine, PhD     Date
Neuropsychology Co-Chair

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APPENDIX VI (8/15/13)

Appendices for RTOG Biospecimen Collection

RTOG BLOOD COLLECTION KIT INSTRUCTIONS
RTOG URINE COLLECTION KIT INSTRUCTIONS

Shipping Instructions:

US Postal Service Mailing Address: For FFPE or Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
UCSF Box 1800
2340 Sutter St, room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
RTOG Biospecimen Resource
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

☐ Include all RTOG paperwork in pocket of biohazard bag.
☐ Check that the ST Form has the consent boxes checked off.
☐ Check that all samples are labeled with RTOG study and case number, and include date of collection as well as collection time point.

☐ FFPE Specimens:
  o Slides should be shipped in a plastic slide holder/ slide box. Place a small wad of padding in top of container. If you can hear the slides shaking they are likely to 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 them shaking they are likely to break during shipping.
  o Slides, Blocks or Plugs can be shipped ambient or with a cold pack either by 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.
  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 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 RTOG Biospecimen Resource by email at: RTOG@ucsf.edu or (415)-476-7864 or fax (415)-476-5271
RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of plasma, or whole blood

Kit contents:
- One Purple Top EDTA tube for plasma (A)
- One Purple Top EDTA tube for Whole Blood (B)
- Twenty (20) 1 ml cryovials
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Kit Instructions
- Specimen Transmittal Form
- UN1845 DRY Ice Sticker
- UN3373 Biological Substance Category B
  Stickers
- Absorbent shipping material (3)
- Biohazard bags (3)

Preparation and Processing of Plasma and Whole Blood:

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

A) Plasma (If requested): Purple Top EDTA tube #1

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

Process:
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 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (up to 10) labeled with RTOG 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 -70 to -90°C until ready to ship on dry ice.
7. See below for storage conditions.

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

B) 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 RTOG study and case number, collection date and time, 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 (up to 5) labeled with RTOG 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°C.
4. Store blood samples frozen -70 to -90°C 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.
**Storage and Shipping:**

**Freezing and Storage:**

- Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- 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 Mon-Tues).
    - 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 Mon-Tues).
    - OR: Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only- Canada Mon-Tues).
- 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 RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all 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 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.**
- For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271

**Shipping Address:** **FedEx/UPS/Courier address** *(For all frozen samples)*

RTOG Biospecimen Resource at UCSF
2340 Sutter St, room S341
San Francisco, CA 94115

Contact Phone 415.476.7864
RTOG 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 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Two 7 ml disposable pipets
- Parafilm for sealing outside of tubes
- Absorbent Paper Towel

Preparation and Processing of Urine Specimens:

- 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 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 RTOG 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 -20°C or -80°C Freezer until ready to ship

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 Mon-Tues).

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 Mon-Tues).
- 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.
- Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and site will be notified.
- Include all RTOG paperwork in a sealed plastic 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 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 ordering, collection, or shipping a Urine Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271

Shipping Address : FedEx/UPS/Courier address (For all frozen samples)

RTOG Biospecimen Resource at UCSF
2340 Sutter St, room S341
San Francisco, CA 94115

Contact Phone 415.476.7864
KEEPING RECORD OF YOUR SEIZURES IS VERY IMPORTANT AND WILL HELP YOUR PHYSICIAN IN MANAGING YOUR SEIZURES. THIS RECORD IS DESIGNED FOR YOU TO ACCURATELY RECORD YOUR SEIZURES AND YOUR MEDICATIONS. A SPACE IS PROVIDED FOR YOU TO COMMENT ON ANY UNUSUAL EVENTS, CHANGES IN MEDICATIONS OR MENSES, OR ANY EVENTS THAT YOU MAY FEEL MIGHT CONTRIBUTE TO SEIZURE ACTIVITY. **PLEASE REMEMBER TO BRING THIS RECORD WITH YOU TO EVERY CLINIC AND HOSPITAL VISIT.**

You will fill out a column for each week of the month by writing in the number times that reflects your seizures for that week.

You will receive enough forms to be completed for each month prior to your next clinic visit and some extras. It is very important that we know the status of your seizures. **Please sign your name and date at the bottom of each page turned in.**

**HAVE YOU HAD ANY SEIZURES DURING THE MONTH OF _____________________?**

<table>
<thead>
<tr>
<th></th>
<th>WEEK 1</th>
<th>WEEK 2</th>
<th>WEEK 3</th>
<th>WEEK 4</th>
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</thead>
<tbody>
<tr>
<td>Type A: grand mal seizure</td>
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<td>Type B: “butterfly” feeling in the stomach, metallic taste in the mouth, progression to loss of awareness</td>
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<tr>
<td>Type C: staring, fumbling with the hands, confusion for 5 – 10 minutes</td>
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<td>Type D: Brief staring spell</td>
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### Anti-Epileptic Medications

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<tr>
<th>Name</th>
<th>Dose</th>
<th>Dosage Schedule</th>
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<tbody>
<tr>
<td>Example: Dilantin</td>
<td>100 mg</td>
<td>200 mg/am and 200 mg/PM = 400 mg/day</td>
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</table>

### Other Medications

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Dosage Schedule</th>
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**Comments**

_________________________________________________________________________________
________________________________________________________________________________________
________________________________________________________________________________________

Patient signature: ___________________________ Date: _______________
APPENDIX VIII (12/3/12)

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU 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 enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members’ area at https://www.ctsu.org

All forms and documents associated with this study can be downloaded from the RTOG-0925 Web page on the CTSU members’ area of the website (https://www.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS.

Requirements for RTOG-0925 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- IRB Approval Letter
- IRB-Approved Consent Form

Pre-study requirements for patient enrollment on RTOG-0925

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.
- Pathology materials submitted per Section 10.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Mon-Fri. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form
   - Eligibility Checklist
   - See protocol Section 12 for all protocol-specific forms to be submitted at time of patient enrollment.

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The RTOG registration desk closes at 5:00 pm Eastern Time. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and will follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the RTOG within the confines of RTOG’s registration hours (9:00 am-5:00 pm Eastern Time) to obtain assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-0925 Web page located on the CTSU members’ area of the website (https://www.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the RTOG unless an alternate location is specified in the protocol. See protocol Section 12 for details. Do not send study data to the CTSU.

3. The RTOG data center will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the RTOG data center and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the RTOG data center.

SPECIAL MATERIALS OR SUBSTUDIES

Specimen Collection for correlatives or banking (Protocol Section 10.0):
- Collect, prepare, and submit specimens as outlined in the protocol
- Do not send specimens, supporting clinical reports, or transmittals to the CTSU

Quality of Life and Neurocognitive Assessments:
- Please consult protocol Section 11.0 for specific information regarding QOL and neurocognitive patient assessments.

SERIOUS ADVERSE EVENT (AE) REPORTING: N/A

DRUG PROCUREMENT: N/A