Official Title: A Single Arm, Pilot Study of Ramipril for Preventing Radiation-Induced Cognitive Decline in Glioblastoma (GBM) Patients Receiving Brain Radiotherapy

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COVER PAGE

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A Single Arm, Pilot Study of Ramipril for Preventing Radiation-Induced Cognitive Decline in Glioblastoma (GBM) Patients Receiving Brain Radiotherapy

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Amendment 4	Version 09/24/2019	Released 03/16/2020
Amendment 5	Version 12/01/2020	Released 02/01/2021
Amendment 6	Version 12/08/2021	Released 03/01/2022

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at https://www.ctsu.org, and select the Regulatory --> Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through REDCap. Refer to the data submission section of the protocol for further instructions. Address: Wake Forest NCORP Research Base Wake Forest Baptist Medical Center Building 525@Vine, 4th floor Medical Center Boulevard Winston-Salem, NC 27157 Fax: (336) 713-6476 Email: NCORP@wakehealth.edu Do **not** submit study data or forms to CTSU Data Operations. Do **not** copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on of the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) contact Wake Forest NCORP Research Base at NCORP@wakehealth.edu. All correspondence will be triaged to the appropriate WF NCORP RB representative.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA

Screen, recruit, consent and **register** patients scheduled to receive partial brain radiotherapy and temozolomide (or chemotherapy) for newly diagnosed Glioblastoma (GBM)

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Baseline: MRI Brain
History and physical, Blood pressure, current medications
Neurocognitive Test Battery
Participant Reported Outcome Questionnaires (PRO)
Blood draw for chemistry, pregnancy test (if applicable) and Apolipoprotein epsilon genotype (ApoE)

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Ramipril capsules daily x (6 weeks of RT course + 4 months)
(Week 1of RT: one 1.25 mg capsule orally once a day)
(Week 2 of RT: two 1.25 mg capsules (2.5 mg total orally once a day)
(Week 3 of RT: four 1.25 mg capsules (5 mg total orally once a day)
Continue on maximally tolerated dose (2.5-5 mg orally once a day) for 4 months post RT

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Interventions

Weeks 1-3:	Administration/titration of study drug, weekly toxicity assessment by Study Team, obtain medication diaries for compliance and verify dosage, blood pressure and blood draw
Weeks 4-5:	Administration of maximally tolerated study drug, weekly toxicity assessment by Study Team, obtain medication diaries for compliance and verify dosage, blood pressure and blood draw.
Week 6 - RT completion:	Administration of maximally tolerated study drug, Study Team toxicity assessment, obtain medication diaries for compliance and verify dosage, blood pressure. Repeat neurocognitive battery and PRO questionnaires.
1 Month Post RT (Wk10):	Administration of maximally tolerated study drug, Study Team toxicity assessment, obtain medication diaries for compliance and verify dosage, blood pressure, MRI brain. Repeat neurocognitive battery and PRO questionnaires
2, 3 Month post RT (Wk 14, 18):	Administration of maximally tolerated study drug, Phone interview for toxicity assessment, verify study medication dosage and compliance (request medication diaries be returned in-person or via mail)
4 Month post RT (Wk 22):	Study Team toxicity assessment, obtain medication diaries for compliance, verify dosage and collect any remaining study medication, blood pressure, MRI brain. Repeat neurocognitive battery and PRO questionnaires
5 Month post RT (Wk 26):	Phone interview for toxicity assessment

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Endpoints

Co-Primary:	Retention rate and Clinical Trial Battery Composite (CTB COMP) score at 1 Month Post RT (Wk 10)
Secondary:	Non-memory cognitive functions: Estimate the effect with Ramipril treatment
	Neurocognitive failure: Estimate time for patients with GBM receiving chemoradiotherapy and Ramipril
	Biomarkers: APOE genotype, a risk factor for cognitive impairment and dementia
	Neurocognitive function: Estimate neurocognitive function in surviving patients at end of study (4 Month Post RT)
	Participant reported outcomes (PRO): Measures physical, emotional, social etc. of patient to complement neurocognitive tests

Study Sample: N=75
Study Duration: Approximately 26 months

Brief Eligibility Criteria: ≥ 18 years old; pathologically proven GBM; planned to receive brain RT and concurrent temozolomide chemotherapy; ECOG 0, 1 or 2; Baseline HVLT-R Delayed Recall score must be submitted.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the retention rate of patients at 10 weeks of Ramipril treatment (6 weeks during RT and 4 weeks post RT) to determine whether or not we should proceed to a subsequent randomized study. Retention is defined by (1) compliance with drug therapy for at least 75% of doses during the 10 week period and (2) completion of the composite neurocognitive battery.

1.1.2 To estimate the effect of 10 weeks of Ramipril on neurocognitive function in patients with GBM receiving chemoradiotherapy. Neurocognitive function is measured by the Clinical Trial Battery Composite (CTB COMP) score.

1.2 Secondary Objectives

1.2.1 To estimate the time to neurocognitive decline with GBM receiving chemoradiotherapy and Ramipril. Decline will be defined as the time at which a change greater than the reliable change index for any of the individual cognitive tests is experienced for a particular patient.

1.2.2 To estimate the effect of treatment with Ramipril on and variability of specific non-memory cognitive functions including attention, executive function, visuo-motor skills, working memory, a screening measure of global cognitive function, mood, quality of life, fatigue and sleep disturbance.

1.2.3 To collect preliminary data on the presence of apolipoprotein epsilon (ApoE) isoform 4 serum (peripheral blood lymphocyte) test positivity as measured by quantitative PCR.[1]

1.2.4 To estimate neurocognitive function in surviving patients at the 4 month post RT endpoint.

1.2.5 To estimate response as reported by treating physician assessments.

1.3 Exploratory Objectives

1.3.1 To explore any subgroup differences for all secondary objectives measured at the post-RT 4 month visit by whether the patient received Optune® (also known as Tumor-Treating Fields or TTFields) as part of their standard treatment following RT.

2. BACKGROUND

2.1 Study Disease

There are approximately 12,000 cases of glioblastoma (GBM) in the US each year.[2] The standard treatment approach includes maximum safe resection followed by radiotherapy (RT) with concurrent and adjuvant temozolomide chemotherapy. **Approximately 30% of these patients will experience significant radiation-induced cognitive decline (RICD) within the first four months after completion of RT**.[3] As with other tumors for which RICD develops, the likelihood and severity of **significant toxicity increase with survival time after brain RT.**[4] The past 2 decades have demonstrated significant therapeutic advances for glioblastoma which have led to a corresponding increase in

survival.[5,6] As a result, a need has arisen to deal with the permanent cognitive toxicities of treatment, and as such, there is a growing interest in the development of cytoprotective agents.

Identification of putative mechanisms of RICD in the brain has created several opportunities for the use of cytoprotective agents, particularly those that mediate oxidative stresses. It has been hypothesized that the reperfusion injury that occurs after radiation-induced ischemia is caused by reactive oxygen species, and that this injury is a major mediator of RICD.[7] The renin angiotensin system (RAS) has been implicated in mediating a pro-inflammatory cascade in the brain that leads to worsening of cognition,[8] and preclinical studies support the role of the RAS in cognitive changes after brain irradiation.[9,10]

Several recent studies have re-purposed pharmaceutical agents known for activity against Alzheimer's dementia (AD) to treat existing RICD. To date, these attempts have met with mixed results. These re-purposed agents have sparse pre-clinical data showing benefit in the brain-irradiated population. The RTOG 0614 trial randomized patients with brain metastases receiving whole brain RT to placebo or 20 mg memantine, a drug used to treat symptoms of AD, starting within the first 3 days of RT. Results revealed that memantine treatment was associated with a non-significant trend in delayed time to cognitive decline and reduced the rate of loss of memory, executive function, and processing speed.[11] Although this trial showed promise, it has been criticized for poor retention of patients due to disease progression and patient death.

Donepezil, an acetylcholinesterase inhibitor used to treat symptoms of AD, was found to have no overall group difference in cognitive functioning but reported significantly improved memory function and motor speed/dexterity in a randomized placebo controlled trial of irradiated brain tumor survivors[12] conducted by our Research Base. Significant interactions between pre-treatment cognitive function and treatment were found for overall cognitive functioning, memory, attention, visuomotor skills and motor speed and dexterity, with results favoring the donepezil group compared with the placebo group in patients with worse baseline function.[12] While these results are promising, donepezil treats symptoms of decline after they occur and seems to improve outcomes in limited populations. It is not a cytoprotective agent that would protect against cognitive decline before it occurs.

Each of the aforementioned investigational agents was chosen because of its efficacy in treating non-cancer-related neurocognitive disorders, such as AD and vascular dementia, and because preclinical data supporting a specific mechanism of RICD had not yet been identified. None of the investigated agents to date have pre-clinical data showing benefit in the brain-irradiated population. The proposed study differs from these studies by targeting a specific mechanism of brain injury which otherwise leads to cognitive dysfunction.

2.2 Study Agent

Interventions: Incorporation of Ramipril as a Cytoprotective Agent
Pre-clinical models have demonstrated that the severity of RICD can be mitigated with use of cytoprotective agents during and after the course of RT, thus preventing the oxidative brain injury that leads to RICD development.[13-17] One such agent, Ramipril, is an angiotensin-converting enzyme inhibitor (ACE-I) that is used to treat hypertension and congestive heart failure. Ramipril acts to negatively regulate the renin angiotensin system (RAS) both systemically and within the central nervous system (CNS). The major effector signal of the RAS is angiotensin II, which acts on AT1 and AT2 receptors. **The RAS is thought to mediate a pro-inflammatory cascade within the brain.** Irradiation of the brain leads to chronic increases in reactive oxygen species and reactive nitrogen oxide species, which leads to progenitor cell death as well as a phenotype of chronic inflammation and organ dysfunction. The high oxygen consumption within the brain, as well as the presence of oxidizable unsaturated fatty acids[18] and free iron,[19] provide an ideal environment for both acute and chronic inflammation.

Within the CNS, the RAS appears to be active within both neuronal and glial cells. AT1 and AT2 receptors are expressed throughout the brain, but are particularly concentrated within the hippocampus,[20] suggesting a mechanism for why Ramipril may be a particularly effective cytoprotective agent for RICD. Damage to the hippocampus is purported to be an important mechanism of radiation brain injury, given its high concentration of neural progenitor cells. There is significant interest in the hippocampus as a target of radiation damage, given the recently published results of the RTOG hippocampal-sparing whole brain RT (HS-WBRT) trial.[21] While the radiation tolerance of the hippocampus and the efficacy of HS-WBRT is still in question, clinical trials have certainly focused on the hippocampus as a viable target structure involved in RICD. A recent dose-volume histogram analysis of patients enrolled in cognitive studies after brain irradiation showed that higher doses to the temporal lobe and hippocampi did lead to poorer cognitive results.[22] Hippocampal sparing RT would be complicated in the primary brain tumor population where many tumors either involve or are in proximity to the hippocampi, precluding safe sparing of these structures. As such, pharmacologic blockade of inflammatory and oxidative pathways within the hippocampi would be of great interest for a clinical study.

Pre-clinical data have shown that a blockade of the RAS cascade can effect changes in both the purported target structures of brain irradiation as well as in the functional capacity of the animal.[10,13,14,23] The data also suggest that **delivery of Ramipril concurrently or soon after RT is critical to optimizing its cytoprotective effects, implying that once brain injury and functional loss has occurred, the cytoprotective window is lost**. Jenrow *et al*. described the use of Ramipril in rats in the immediate post-radiation setting and then for 12 consecutive weeks after brain RT. Subsequent immunohistochemical studies revealed that Ramipril mitigates the decrease in neurogenesis seen in the rat dentate gyrus of the hippocampus after whole brain RT and that it does so by preventing apoptosis in progenitor cells.[13] Given that apoptosis is an acute response to radiotherapy, the findings imply that earlier treatment with Ramipril after RT is critical to its effectiveness. In another study, Lee *et al*. demonstrated that use of Ramipril prior to, concurrent with, and after whole brain RT was able to ameliorate RICD in rats.[10] The novel object recognition test, a test of hippocampal dependent memory, was used to assess for RICD in this study. A specific study of the timing of Ramipril administration on its radioprotective ability in the CNS showed that earlier treatment with Ramipril yields better functional neurologic outcomes.[23]

Advantages of Ramipril as a potential neuroprotective agent are its known penetration across the blood brain barrier and its established tolerability. Ramipril's lipophilicity allows for its ability to cross the blood brain barrier. Kinetic studies of Ramipril have been performed in dogs where measurable concentrations of Ramipril and its active diacid form, were detected in CSF after administration of oral Ramipril.[15] A 100% converting enzyme blockade in the plasma of rats has been correlated with an 84% inhibition of converting enzyme activity in the corresponding cerebrospinal fluid, demonstrating the drug's passage through blood brain barrier and inhibition of central converting enzyme activity.

In clinical studies involving humans, Ramipril has been reported to positively affect cerebral blood flow in elderly patients with carotid artery occlusive disease at a dose of 5mg.[16] Davies *et al*. reported in a nested analysis that patients with AD were less likely to have been prescribed an ARB (Angiotensin Receptor Blocker) or ACE-I,[24] suggesting that it is possible that there may be a lower rate of AD diagnoses in patients who had been prescribed an ARB or ACE-I. Furthermore, a pilot study showed that Ramipril administered at 5mg dose inhibited CSF ACE activity, demonstrating that clinically relevant doses of Ramipril cross the blood brain barrier.[25] Studies in patients at risk of AD[25] and patients with cardiovascular disease[26] show no direct change in cognition caused by administration of Ramipril – again suggesting that Ramipril's benefits are considered to be prophylactic as opposed to therapeutic.

The toxicity profile of Ramipril has been evaluated in normotensive patients.[27] Ramipril has a risk of cough (7-12% incidence), an 11% rate of hypotension, 2% risk of orthostatic hypotension, and up to a 2%

risk of syncope. Other less common side effects include headache (1-5%), dizziness (2-4%), and 2% or less of fatigue, nausea or vomiting. Non-cardiac chest pain (1%), increase in serum creatinine in normotensive patients (1%) and hyperkalemia (1-10%) have also been reported.[16] Ramipril has not demonstrated tumor protective or tumor promoting activities, and population studies have shown a lower risk of cancer in patients on ACE inhibitors.[28] Ramipril's cytoprotective effects have not been shown to extend to protection of tumor in preclinical models.[29] Overall, **Ramipril is thought to be safe and it is widely used worldwide for several indications**. To assess how common pre-existing ACE-I or ARB use is in patients with newly diagnosed glioblastoma, an internal review of patients enrolled on similar trials[30] in the Wake Forest Research Base was conducted. In these studies, 4-12% of patients were already taking an ARB or ACE-I for other indications at the time or enrollment.

Correlative science: Finding markers of susceptibility
A translational goal of this study is to learn more about biological and non-biological vulnerability factors that may influence the severity of cognitive decline in relation to RT and response to treatment. Including several biological and non-biological markers for cognitive vulnerability will help to identify patients who are at greater risk of developing cognitive problems as well as increase our understanding of the underlying mechanisms of neurocognitive dysfunction associated with cancer and its treatments, which may further elucidate therapies targeted specifically to mechanism.

Apolipoprotein E (APOE) genotype, **older age**, and lower **baseline cognitive performance** are all associated with a greater risk of developing AD and of transition from mild cognitive impairment to AD and thus may also identify brain tumor survivors who are at greater risk of developing cognitive decline. The ApoE gene is responsible for producing factors important for remodeling and repairing neurons in response to injury or stress. There have been other clinical studies relating ApoE4 allele status with increased atrophy of parenchymal brain tissues, particularly in the hippocampus. Carriers of the epsilon 4 (Ɛ4) alleles are at higher risk for developing AD and converting from mild cognitive impairment (MCI) syndrome to AD. ApoE 4 has been implicated in mediating both chemotherapy-induced cognitive decline[31] and RICD.[32] Thus, ApoE 4 allele carrier status is a genetic marker for cognitive vulnerability; as such, it may be useful in predicting which patients are most susceptible to the adverse cognitive effects of RT. While the proposed sample size will restrict our power to test the influence of ApoE, we will perform exploratory analyses to determine the strength of association. Also, we are collecting ApoE status in other Research Base studies of radiation-associated cognitive impairment so we may eventually be able to conduct analyses pooled over multiple studies.

Cognitive reserve (CR) refers to acquired compensatory strategies that enhance a person's cognitive and behavioral capacities.[33,34] Individuals with higher CR should have less impairment because of their greater adaptive capacity. Common proxies for CR are literacy and educational and occupational attainment. Higher levels of CR have been associated with lower incident rates of age-associated cognitive impairment and longer delayed onset of dementia. CR will be examined as a susceptibility factor for RICD (we hypothesize that low CR individuals will have greater cognitive impairment at baseline than higher CR individuals).

In summary, RICD is a common problem following brain RT for GBM. It can affect various cognitive functions, and generally does not have a plateau in terms of severity after onset. Preclinical models suggest that by modifying the RAS within the brain, one can mitigate the inflammatory cascade that ultimately leads to RICD. Ramipril is a widely used safe and tolerable ACE-I that penetrates the blood brain barrier. The Wake Forest NCORP Research Base has a long history of evaluating pharmaceutical interventions that may mitigate symptoms of RICD, demonstrating our ability to conduct this current study. This proposal represents collaboration between Wake Forest investigators and the neurocognitive experts involved in the RTOG 0825 study. RTOG 0825 was a prospective, randomized phase III trial in newly diagnosed patients with glioblastoma comparing standard radiation and temozolomide therapy with

and without bevacizumab. RTOG 0825 also prospectively collected extensive neurocognitive data on all enrolled patients. The eligibility criteria and planned combined modality treatment proposed in this trial are identical to that used for the cohort of patients treated on the control arm of RTOG 0825. Furthermore, the neurocognitive battery and times of administration proposed in this study have been harmonized with the battery and schedule utilized in RTOG 0825 thus providing an ideal modern era historical control group to appropriately compare with this pilot study population and ensure an ability to interpret the results of our proposed trial in the context of the most current understanding and effect magnitude of RICD in the GBM population.

2.3 Rationale

Significance of the Proposed Study
The proposed study will positively impact current research into RICD and cytoprotection. It is based on compelling pre-clinical data from the use of Ramipril and other RAS modifiers for this indication. This study includes patients with GBM, the most common primary brain tumor and therefore the most common indication for partial brain irradiation. Moreover, it leverages the strong accrual history of the Wake Forest NCORP neurocognitive trial portfolio, the collaborative neurocognitive expertise from NRG and Wake Forest, and the enormous investment of time, money, energy and patients already made in the collection of the RTOG 0825 neurocognitive dataset. The NRG has already agreed to grant us access to the data from RTOG 0825 to use as a comparison data set for analysis once this trial is completed.

A positive finding in our study would serve as proof of principle for the hypothesis that the angiotensin II pathway is important in RICD. This study will provide data to support the design of a larger, randomized trial to assess the effect of an ACE-I during RT. The current trial has been designed for patients with GBM because of the relatively homogeneous population and treatment approach, and the known time course of cognitive decline after RT.[35] However, should Ramipril succeed in mitigating RICD in the GBM population, this treatment could then ultimately be investigated in a much larger population of brain irradiated individuals including patients with lower grade gliomas, benign brain tumors, and brain metastases.

Feasibility
The sample size for this study will be 75 patients. Accrual is expected to average ~4 participants per month, so target accrual should be met within 20 months. Based on experience, sites will slowly ramp up accrual as protocol familiarity is attained. Thus, we propose the following cumulative recruitment goals: Q1 – 4, Q2 – 12, Q3 – 22, Q4 – 34, Q5 – 48, Q6 – 62, Q7 – 75. Participants will be followed for up to 6 months, after which, the participant is no longer followed and data is no longer collected.

We anticipate that this pilot study will be feasible based on prior experience, with an expected accrual of four patients per month. We have previously conducted a trial (CCCWFU 97600)[36] assessing HRQOL and cognition in brain tumor patients undergoing radiation. Accrual was low in that study (2.2 patients/month), but we only had 4 accruing sites. By the time we completed a subsequent trial assessing memory and cognition in brain tumor survivors (CCCWFU 91105)[12], we had over 20 accruing sites with a combined average of 4 patients per month; therefore showing this average to be achievable. Funding for the study will derive from the Wake Forest NCORP Research Base grant.

3. SUMMARY OF STUDY PLAN

Study design: This is a single arm pilot study of Ramipril 2.5-5mg to prevent cognitive decline in patients receiving partial brain RT.

Number of participants to be enrolled: The sample size for this study will be 75 patients.

Study population: Patients with GBM receiving radiation with concurrent and adjuvant temozolomide per the RTOG 0825 standard arm.

Intervention plan: Patients will be treated with Ramipril (weekly titration from 1.25 mg x 7 days, 2.5 mg x 7 days, then 5 mg x 7 days, titration to highest tolerable dose of at least 2.5 mg) for the length of RT plus four additional months. Each pill will be 1.25 mg, and dosage will be titrated to the correct number of 1.25 mg pills desired. The Ramipril will be dispensed as a titration starting the day of first RT treatment with prescribed doses of 1.25 mg daily (one capsule daily) for 7 days, 2.5 mg daily (2 capsules daily) for 7 days and 5 mg daily (4 capsules daily) for 7 days until completion of drug intake on study. The dose selection was made because 2.5-5mg is effective in vascular protection but less likely to cause syncope or other adverse side effects. This dose level is similar to its use for hypertension. The medication will be titrated to tolerance and taken each evening during the course of RT (starting on the first day) and continued for an additional four months, after completion of RT. The titration of the medication is expected to be complete within the first 3-4 weeks of RT and the Ramipril will continue at the same dose through the remaining RT and for an additional four months after RT. Blood pressure and blood chemistry (creatinine, potassium, and Glomerular Filtration Rate (GFR) will be checked weekly during the titration period prior to titrating to the next dose. Ramipril dose will not be increased any further if any of the following conditions are met: 1) the systolic blood pressure is less than 100 mm Hg, 2) the serum creatinine increases to above the upper limit of normal of either the local institutional lab or LabCorp (LabCorp normal creatinine value range is 0.76-1.27), or if the creatinine remains below the upper limit of normal but has increased >/= to 100% of the previous week's value from the same lab, 3) serum potassium rises above 5.0 mEq/L or 4) Grade 3 or greater toxicity attributable to drug (possible, probable or definite) is identified during weekly toxicity evaluation.

If an institutional creatinine result is used to guide Ramipril titration, then the upper limit of normal of the institutional lab should be used to guide titration as described above. Either the local institutional lab or LabCorp lab should be chosen and used for <u>all</u> Week 1-6 visits to be consistent with the normal values used during the titration period. If choosing to use local institutional labs for Week 1-6 visits, please also draw and submit research LabCorp labs to allow for comparison across study sites.

After RT is completed, patients will have a monthly phone call by study staff to assess for symptoms, medicine changes, compliance and toxicity on post RT month 2 and 3. On post RT month 4 (Week 22), patients will have a face-to-face visit with study staff to assess for symptoms, medicine changes, compliance and toxicity. Ramipril treatment may be terminated early if intercurrent illness occurs that prevents further administration, unacceptable adverse events occur, the patient decides to withdraw from the study or if changes in the patient's condition occur to render the patient unacceptable for further treatment in the judgment of the investigator. Patients will be followed for 30-days post Ramipril treatment ending with a phone call and toxicity assessment on the last study visit 5-month post RT (Week 26).

Chemoradiotherapy: Chemoradiotherapy will be performed using the same protocol as the standard arm of the RTOG 0825 study. 60 Gy Total dose will be delivered to the contrast-enhanced volume + 2 cm CTV margin. The FLAIR or T2 volume will receive 46 Gy + 2.5 cm margin. Dose limitations to critical structures will also be identical. Temozolomide will be administered daily and continuously starting on day 1 of radiotherapy and be given for a maximum of 49 days at a dose of 75 mg/m2. Adjuvant temozolomide will be administered 5 consecutive days on days 1-5 of a 28-day cycle for 6 cycles at a starting dose of 150 mg/m2. As per standard practice and in the absence of myelosuppression with cycle #1, the dose of temozolomide will be titrated upward to 200mg/m2/d for cycles #2-6. Dose adjustments

by the treating physician will be allowed as per standard practice outlined in the official product monograph.

Every effort should be made to begin the standard of care temozolomide on the first day of radiation therapy. It is understood, however, that insurance and pharmacy related issues often delay the receipt of temozolomide by these patients and, as a result, despite best efforts, in some cases the start of chemotherapy may be delayed into the first or second week of radiation. Patients who cannot begin the temozolomide within the first 3 weeks (15 fractions) of radiation will be considered ineligible and will need to be removed from the study.

Optune® (TTFields): Optune® is a portable battery or power supply-operated device which produces alternating electrical fields, called tumor treating fields ("TTFields"), applied to the brain through transducer arrays placed on the scalp which disrupt the rapid cell division exhibited by cancer cells.[37] The TTField technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be unaffected by the TTFields. Optune® with temozolomide is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care temozolomide chemotherapy. This approval followed the release and subsequent publication by Stupp R, *et al*. of the results of a prospective randomized clinical trial in 695 patients with newly diagnosed glioblastoma of maintenance temozolomide with or without the Optune® device.[38] The median survival in the device plus temozolomide arm was 20.9 months vs. 16.0 months in the temozolomide alone arm (HR, 0.63; 95% CI 0.53-0.76; p<.001).

Optune® with adjuvant temozolomide in patients with newly diagnosed supratentorial glioblastoma is listed as a level 1 recommendation by the NCCN guidelines and has been adopted by many, but not nearly all, medical practitioners who treat these patients. Currently, a minority of newly diagnosed glioblastoma patients are either offered or choose to accept this treatment modality due to patient or provider preferences, or established contraindications to use which include the presence of implantable electronic devices, allergy to the array's conductive hydrogel adhesive or the presence of cranial defects. Optune® may only be prescribed by qualified physicians who have completed a training course given by Novocure (the device manufacturer). Of note, as prescribed in the pivotal clinical trial referenced above[38], standard practice is to apply the Optune® device no sooner than 4 weeks after the completion of concurrent radiation and temozolomide chemotherapy.

For patients enrolled on this trial, Optune® may be used at the discretion of the treating physicians as per standard of care guidelines, timing and training. Use will be captured and an exploratory analysis of primary and secondary objectives based on the subgroups using and not using the device will be performed.

Drug: Ramipril (e.g.Altace® or Tritace®) is an ACE-I. It is currently FDA approved for use in the treatment of hypertension and for reducing the risk of myocardial infarction, stroke and death from cardiovascular causes. The drug will be obtained, packaged, and distributed by McKesson Corporation (Winston-Salem, NC). McKesson Corp. will also provide storage and inventory for the study drug. Ramipril will be provided to study participants at no cost.

Assessment plan: Participants will complete the entire battery of neurocognitive tests and questionnaires measuring cognitive symptoms, mood, fatigue, sleep disturbance and quality of life at baseline, at the completion of RT, 1 month post-RT, and q3 monthly thereafter up to 4 months post-RT or until time of

tumor progression. At the end of radiation and at the one and four-month post-RT follow-up visit, patients' tolerance of medication and compliance will be assessed by a research team member at an in-person visit coordinated with clinical follow-up. Patients are encouraged to call at any time for questions regarding study drug and will fill out a diary to document study drug compliance.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 Histologically proven diagnosis of glioblastoma or gliosarcoma (WHO grade IV) obtained at the time of a partial or gross total resection of the tumor. Patients who undergo a stereotactic needle biopsy alone are not eligible.

4.1.2 The tumor must have a supratentorial component.

4.1.3 History/physical examination within 14 days prior to enrollment

4.1.4 The patient must have recovered from the effects of surgery, postoperative infection, and other complications before enrollment.

4.1.5 Patient planning to receive brain RT, and concurrent and adjuvant temozolomide chemotherapy for 6 weeks as per standard of care therapy. Use of the Optune® (also known as Tumor Treating Fields or TTFields) device is allowed at provider discretion, but must begin after the Month 1 Post RT (10 wk) Neurocognitive-PRO assessment.

4.1.6 Study drug (Ramipril) must be given ≥ 21 days and ≤ 42 days after surgery.

4.1.7 All available brain MRI or CT imaging reports from surgery to study completion must be submitted. This includes any post-operative or pre-radiation scan reports.

4.1.8 ECOG 0, 1 or 2;

4.1.9 Age ≥ 18;

4.1.10 CBC/differential obtained within 14 days prior to enrollment, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥10.0 g/dl is acceptable.)

4.1.11 Adequate renal function, as defined below:

- BUN ≤ 30 mg/dl within 14 days prior to enrollment.
- Creatinine ≤ 1.7 mg/dl within 14 days prior to enrollment.

4.1.12 Adequate hepatic function, as defined below:

- Total Bilirubin ≤ 2.0 mg/dl within 14 days prior to enrollment.
- ALT/AST ≤ 3 x normal range within 14 days prior to enrollment.

4.1.13 Patient must provide study specific informed consent prior to study entry.

4.1.14 Baseline potassium level < 5.0 mEq/L. High potassium values that are thought to be a result of sample hemolysis may be repeated to determine an accurate potassium level and to determine potential study eligibility. Likewise high potassium values thought to be a result of potassium supplementation may be repeated at an appropriate time (5 half-lives after supplement discontinuation) to determine potential study eligibility.

4.1.15 Patient must be able to complete neurocognitive tests in the English language as they are not validated in other languages at this time.

4.1.16 Women of childbearing potential and male participants must practice adequate contraception.

4.1.17 For females of child-bearing potential, negative serum or urine pregnancy test within 14 days of enrollment

4.1.18 Local site must be able to follow the standard GBM radiation treatment dosimetry plan as detailed in Section 5.1.1.2

4.1.19 For patients who will be treated with the Optune® device in addition to standard of care radiation plus concurrent and adjuvant temozolomide, the following inclusion criteria also apply:

- Patients must have only a supratentorial glioblastoma
- The treating physician must be a qualified provider having successfully completed the training course provided by Novocure, the device manufacturer

4.1.20 Patients with prior malignancies if all treatment for that malignancy was completed at least 2 years before registration and the patient has no evidence of disease.[56]

4.2 Exclusion Criteria

4.2.1 Prior allergic reaction or intolerance to ACE inhibitor

4.2.2 Hypotension (<110 mg Hg systolic) at the time of enrollment

4.2.3 Renal insufficiency with creatinine clearance of <40 ml/min (at time of enrollment)

4.2.4 Solitary kidney or known renal artery stenosis

4.2.5 Current ACE inhibitor or angiotensin receptor blocker use. Patients can come off ACE inhibitors or angiotensin receptor blockers for 1 week to be eligible for this study.

4.2.6 Prior invasive malignancy (except for non-melanomatous skin cancer) unless disease free for ≥ 2 years. (For example, carcinoma in situ of the breast, oral cavity, and cervix are all permissible).

4.2.7 Recurrent or multifocal malignant gliomas

4.2.8 Metastases detected below the tentorium or beyond the cranial vault.

4.2.9 Prior chemotherapy or radiosensitizers for cancers of the head and neck region; note that prior chemotherapy for a different cancer is allowable, except prior temozolomide. Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment are not permitted.

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

4.2.11 Severe, active co-morbidity, defined as follows:

- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of enrollment
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of enrollment.
- Known HIV positivity or acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
- Active connective tissue disorders, such as lupus or scleroderma, that in the opinion of the treating physician may put the patient at high risk for radiation toxicity.
- Any other major medical illnesses or psychiatric impairments that in the investigator's opinion will prevent administration or completion of protocol therapy.

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

4.2.13 Pregnant or lactating women, due to possible adverse effects on the developing fetus or infant due to study drug.

4.2.14 Patients treated on any other therapeutic clinical protocols within 30 days prior to study entry or during participation in the study unless they involve standard of care or over the counter therapies or do not involve a drug therapy. Questions regarding eligibility for patients enrolled on other therapeutic clinical trials should be forwarded to the Wake Forest NCORP Research Base email (NCORP@wakehealth.edu) for review.

4.2.15 Patients planning to receive therapeutic antitumor agents (excluding use of the Tumor Treating Fields (TTFields or Optune®) device after the Month 1 Post RT (10 wk) Neurocognitive-PRO assessment) in addition to standard radiation and concurrent and adjuvant temozolomide are not eligible to participate in this study.

4.2.16 Patients with impaired decision-making capacity; this exclusion is necessary because such patients may not be able to adequately give informed consent.

4.2.17 For patients who will be treated with the Optune® device in addition to standard of care radiation plus concurrent and adjuvant temozolomide, the following exclusion criteria also apply:

- Optune® is not permitted in patients who have an active implanted medical device, skull defect (such as, missing bone with no replacement) or bullet fragments. Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmatic shunts.
- Optune® is not permitted in patients who are known to be sensitive to conductive hydrogels. Examples of conductive hydrogels are gels used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes.

4.2.18 Patients being treated with Memantine, Donepezil, and/or other medications prescribed to enhance cognition.

4.3 Inclusion of Women and Minorities

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

4.4 Recruitment and Retention Plan

4.4.1 Patients with newly diagnosed glioblastoma will be identified by a member of their medical or local research team at each participating Research Base NCORP site. They may review cancer registry and medical chart information to identify patients eligible for this protocol. Patients identified will be asked about their interest in participating in a study of the cognitive effects of chemoradiotherapy in clinic or by a letter from their physician informing them about the study, and indicating that a research team member will be calling to tell them more about the study. Patients identified and spoken to by the study team should be added to the Screening Log (Appendix C). Accrual is expected to be 4 patients per month. Targeted accrual should be met in approximately 20 months. A maximum of 75 patients will be enrolled on this trial. Patients found to be eligible will be followed for up to 7 months. After the 5 month post RT phone call, the patient is no longer followed and data is no longer collected from the patient.

4.4.2 Patients who meet eligibility criteria will be invited to participate in this clinical trial of a drug to improve cognitive functioning. Eligible patients will be administered the informed consent form (ICF). Screening logs are to be submitted to Wake Forest NCORP Research Base at the end of each month.

4.4.3 Patients who meet all eligibility criteria and sign the ICF will be scheduled for a face-to-face assessment session during which baseline measures will be collected; for some patients this will occur at the screening visit. A research nurse or similarly qualified and trained individual will administer the battery of cognitive tests and questionnaires. Socio-demographics and health status will also be collected.

4.4.4 The WF NCORP Research Base currently has 43 participating NCORPs inclusive of 14 NCORP-MUs located in 42 states, the District of Columbia and two U.S. territories (Guam and Puerto Rico), in addition to Wake Forest Baptist Medical Center. We will recruit participants from all

sites within the WF NCORP Research Base network who choose to participate in this trial. Sites will be required to have a centrally trained and certified examiner for Neurocognitive Assessments and Participant reported outcomes (PRO) (see Section 7.6.1 for details). There are no other WF NCORP Research Base studies currently open or planned that will compete with this study. A total N of 75 is likely to be enrolled after approximately 20 months. Each participant will be followed for 7 months. Estimated duration of study is approximately 26 months. Each participant will have 4 clinic visits (Baseline, Post RT (6 Wk), 1- and 4-months post-RT).

4.4.5 To ensure we meet or exceed our minority accrual goals, we will provide administrative guidance, as requested, to the 14 NCORP-MU sites in the WF NCORP Research Base and leverage their experiences to develop best practices for minority accrual that can be shared among all participating sites. Please refer to the table below.

Racial Categories	Not Hispanic or Latino: Female	Not Hispanic or Latino: Male	Hispanic or Latino: Female	Hispanic or Latino: Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	1	1	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	3	0	0	4
White	27	40	1	1	69
More Than One Race	0	0	0	0	0
Total	29	44	1	1	75

5 AGENT ADMINISTRATION

5.1 Dose Regimens

5.1.1 Chemoradiation Therapy

5.1.1.1 Temozolomide

Temozolomide will be administered daily and continuously starting on day 1 of radiotherapy and be given for a maximum of 49 days at a dose of 75 mg/m2. Adjuvant temozolomide will be administered 5 consecutive days on days 1-5 of a 28-day cycle for 6 cycles at a starting dose per package insert. As per standard practice and in the absence of myelosuppression with cycle #1, the dose of temozolomide may be titrated upward as per package insert for cycles #2-6. Every effort should be made to begin the standard of

care temozolomide on the first day of radiation therapy. It is understood, however, that insurance and pharmacy related issues often delay the receipt of temozolomide by these patients and, as a result, despite best efforts, in some cases the start of chemotherapy may be delayed into the first or second week of radiation. Patients who cannot begin the temozolomide within the first 3 weeks (15 fractions) of radiation will be considered ineligible and will need to be removed from the study.

5.1.1.2 Radiation Therapy

Note: Intensity Modulated RT (IMRT) Is Allowed
Modality chosen at registration must be used for the entire course of treatment.

Treatment must begin ≥ 21 days and ≤ 42 days after surgery.

Dose Specifications and Schedule

For both IMRT and 3D-CRT plans, one treatment of 2 Gy will be given daily 5 days per week for a total of 60 Gy over 6 weeks. All portals shall be treated during each treatment session. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are necessary to make this selection.

Technical Factors
Treatment shall be delivered with megavoltage machines of a minimum energy of 6 MV photons. Selection of the appropriate photon energy (ies) should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Electron, particle, or implant boost is not permissible. IMRT delivery will require megavoltage radiation therapy machines of energy ≥ 6 MV.

Localization, Simulation, and Immobilization
The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device to ensure adequate immobilization during therapy and ensure reproducibility is strongly recommended. Simulation may include a dedicated radiotherapy simulator or a virtual simulation using a treatment planning CT. Fusion with MR images is strongly recommended, whenever feasible.

For patients accrued to the protocol, treatment verification and documentation should be carried out, at least for the first treatment fraction, and more frequently, based on institutional policy; weekly verification is common. We suggest orthogonal images for documenting isocenter setup accuracy for the first fraction. These orthogonal images can be obtained with film or EPID. Other imaging techniques are possible, for example, the BrainLab ExacTrac system that uses two orthogonal imaging panels irradiated with KV x-rays. Another example is the volume images obtained with cone-beam CT, or helical tomotherapy or any other CT capability that is integrated with the treatment unit.

Treatment Planning/Target Volumes
Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. Intensity-modulated inverse-planned approaches are permitted. Any of the methods of IMRT (including tomotherapy) may be used, subject to protocol localization and dosimetry constraints. CT-based treatment planning is necessary to assure accuracy in the selection of field arrangements. MRI-fusion for accurate target delineation is strongly recommended.

Initial Target Volume: Target volumes will be based upon postoperative-enhanced MRI. Preoperative imaging should be used for correlation and improved identification. Two planning target volumes (PTV) will be defined, as outlined below. The initial gross tumor volume (GTV1) will be defined by either the T2 or the FLAIR abnormality on the postoperative MRI scan. This must also include all postoperative-enhanced MRI enhancement, and the surgical cavity. The initial clinical target volume (CTV1) will be the GTV plus a margin of 2 cm. If no surrounding edema is present, the initial planning target volume (PTV1) should include the contrast-enhancing lesion (and should include the surgical resection cavity) plus a 2.5-cm margin. The CTV1 margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary. The initial planning target volume (PTV1) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined, along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV ($PTV_{overlap}$), defined as the overlap between the PTV1 and the particular PRV of concern, may be created. Dose to the $PTV_{overlap}$ must be as close as permissible to 46 Gy while not exceeding the OAR dose limit.

Boost Target Volume: The boost gross tumor volume (GTV2) will be defined by the contrast-enhanced T1 abnormality on the post-operative MRI scan. This must also include the surgical cavity margins. The boost clinical target volume (CTV2) will be the GTV plus a margin of 2 cm. The CTV2 margin may be reduced to 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, if necessary. The boost planning target volume (PTV2) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined, along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV ($PTV_{overlap}$), defined as the overlap between the PTV2 and the particular PRV of concern, may be created (the overlap is the intersection between the PTV1 and the PRV). Dose to the $PTV_{overlap}$ must be as close as permissible to 14 Gy while not exceeding the OAR dose limit.

Dose Guidelines: The initial target volume will be treated to 46 Gy in 23 fractions. After 46 Gy, the conedown or boost volume will be treated to a total of 60 Gy, with seven additional fractions of 2 Gy each (14 Gy boost dose).

Isodose distributions for the initial target volume (PTV1) and the conedown target volume (PTV2) are required on all patients. A composite plan is required showing the respective target volumes. The following composite isodose lines should be included: 66 Gy (when 66 Gy dose regions exist in the tumor), 60 Gy, 57 Gy, 48 Gy, 44 Gy and 40 Gy. The inhomogeneity within the target volume shall be kept to ± 10% of the prescribed dose.

The minimum dose to the target volume should be kept within 10% of the dose at the center of the volume. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are encouraged to make this selection.

Dose Limitation to Critical Structures

In addition to the above defined GTVs, CTVs and PTVs the lenses of both eyes, both retinae, both optic nerves, the optic chiasm, and the brainstem must be defined. The maximum point (defined as a volume greater than 0.03 cc) doses permissible to the structures are listed in the table below.

Critical Structure	Maximum Dose
Lenses	7 Gy
Retinae	50 Gy
Optic Nerves	55 Gy
Optic Chiasm	56 Gy
Brainstem	60 Gy

Compliance Criteria

Per Protocol
95% of PTV2 is covered by 60 Gy
99% of PTV2 is covered by 54 Gy

Variation Acceptable
90% of PTV2 is covered by 60 Gy
97% of PTV2 is covered by 54 Gy

Deviation Unacceptable
<90% of PTV2 is covered by 60 Gy
<97% of PTV2 is covered by 54 Gy

It is strongly recommended that any interruptions in the course of radiation be limited to less than 8 days.

Radiation Therapy Adverse Events

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

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

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

5.1.1.3 Optune® (Tumor Treating Fields or TTFields)

Use of the Optune® device is allowed after the Month 1 Post RT (10 wk) Neurocognitive-PRO assessment within this study as long as all additional Optune®-specific inclusion and exclusion criteria are met. Optune® with adjuvant temozolomide in patients with newly diagnosed supratentorial glioblastoma is listed as a level 1 recommendation by the NCCN guidelines and has been adopted by many, but not nearly all, medical practitioners who treat these patients. Optune® may only be prescribed by qualified physicians who have completed a training course given by Novocure (the device manufacturer). Of note, as per the pivotal clinical trial by Stupp R. *et al*.[38], standard practice is to apply the Optune® device no sooner than 4 weeks after the completion of concurrent radiation and temozolomide chemotherapy. For patients enrolled on this trial, Optune® may be used at the discretion of the treating physicians as per standard of care guidelines, timing and training. Use will be captured and an exploratory analysis of primary and secondary objectives based on the subgroups using and not using the device will be performed.

5.1.2 Ramipril

Ramipril (e.g.Altace® or Tritace®) is an ACE-I. It is currently FDA approved for use in the treatment of hypertension and for reducing the risk of myocardial infarction, stroke and death from cardiovascular causes.

Study intervention (Ramipril) will be administered on an *outpatient* basis. Reported AEs and potential risks are described in Section 6.2.

- Ramipril will be taken once daily by mouth

- Weeks 1-3 titration of Ramipril during RT
  - weekly titration from 1.25 mg x 7 days, 2.5 mg x 7 days, then 5 mg x 7 days,
  - titration to highest tolerable dose of at least 2.5 mg daily
- Weeks 4-6 until 4 months post RT
  - highest tolerable dose of at least 2.5 mg daily.
  - highest allowable dose of Ramipril for this study will be 5 mg daily.

Current Ramipril dose should be continued until local institutional lab or research LabCorp lab results are received, which should be used to evaluate toxicities during Weeks 1-6 of RT (see Section 5.2 for further guidance). During Weeks 1-6 of RT, LabCorp and/or local institutional labs should be drawn only after ≥ 4 doses of current Ramipril dose have been taken by the patient. If local institutional labs are going to be used for toxicity assessments, please use them for all Week 1-6 visits for consistency and also draw research LabCorp labs to allow for comparison of
labs across sites. At 1 month post-RT, standard of care local institutional labs will be used to evaluate toxicities per protocol. In the event of inability to obtain LabCorp results in an appropriate time interval, local standard of care labs can be used for Ramipril titration decision making and other protocol related activities.

If lab abnormalities are detected that would affect the conduct of the study, treating physicians should consider whether correctable disease or treatment related toxicities (e.g. dehydration, nausea and vomiting, etc.) could be responsible. If so, clinicians should attempt to address those issues and repeat the labs within 24-48 hours for protocol decision making.

5.2 Ramipril Administration

- Drug will be self-administered orally on an outpatient basis. Ramipril should be taken before bedtime, with or without food.
- Titration of Ramipril will be performed by the local investigator. The medication will be titrated to tolerance and taken each evening during the course of RT (starting on the first day +/- 3 days) and continued for an additional four months <u>after</u> completion of RT.
  - If patients are taking pre-existing anti-hypertensive medications, the treating oncologist (possibly in conjunction with the patient's primary care physician) may modify the pre-existing anti-hypertensive regimen if there is a concern that the addition or titration of Ramipril may lead to hypotension.
  - Blood pressure and blood chemistry (creatinine, potassium, and GFR) will be checked weekly during titration period prior to titrating to the next dose. Ramipril dose will not be increased any further during titration if any of the following conditions are met:
    - systolic blood pressure is less than 100 mm Hg,
    - serum creatinine increases to above the upper limit of normal of either the local institutional lab or LabCorp (LabCorp normal creatinine value range is 0.76-1.27), or if the creatinine remains below the upper limit of normal but has increased >/= to 100% of the previous week's value from the same lab.
      - If an institutional creatinine result is used to guide Ramipril titration then the upper limit of normal of the institutional lab should be used to guide titration as described above.
      - <u>Either the local institutional lab or LabCorp lab should be chosen and used for all Week 1-6 visits to be consistent with the normal values</u>

used during the titration period. However, if in the event of inability to obtain LabCorp results in an appropriate time interval, local standard of care labs can be used for Ramipril titration decision making and other protocol related activities.

- If choosing to use local institutional labs for Week 1-6 visits, please also draw and submit research LabCorp labs to allow for comparison across study sites.

- serum potassium rises above 5.0 mEq/L,
- Grade 3 or greater toxicity attributable to drug is identified during weekly toxicity evaluation.

- Following lack of significant toxicity (including laboratory and blood pressure) review after week 1, patients will take two 1.25 mg capsules of Ramipril (2.5 mg total) per day. Following lack of significant toxicity review after week 2, patients will take four 1.25 mg capsules (5 mg total) per day. The titration of the medication is expected to be complete within the first 3-4 weeks of RT and the Ramipril will continue at the same dose during the remainder of RT and for an additional four months after RT.

- Ramipril treatment may be terminated early if intercurrent illness occurs that prevents further administration, unacceptable adverse events occur, the patient decides to withdraw from the study or if changes in the patient's condition occur to render the patient unacceptable for further treatment in the judgment of the investigator. Refer to Section 8.3 Off-Agent for guidelines.

- Delays in radiation therapy will not affect Ramipril dose titration. If radiotherapy is delayed, the patient will continue on their current dose of Ramipril, or the dose of Ramipril could be reduced as per the above criteria if a significant toxicity occurred. If there is a delay in radiotherapy, patient would still continue Ramipril until 4-months post RT, which could mean the study visits may be pushed out the number of days of the delay. For example, if there is a 1 week RT delay, the patient would have the 1 month-Post RT visit at Week 11, instead of Week 10. A final toxicity assessment will be done by phone at 5 months post RT (Week 26).

If the patient misses a dose of study medication and if it is less than 4 hours late, have them take that dose of study medication as directed. If the patient misses a dose of study medication and if it is greater than 4 hours, do not have them take this dose. Have them take their regular dose at the usual time the following day. If more than one day is missed of study medication, please have them continue as soon as possible. Any missed doses of study medication should be documented on their patient diary.

5.3 Contraindications

While taking Ramipril the following dietary restrictions should be followed:

- Drink adequate water to avoid the risk of dehydration
- Avoid salt substitutes that are high in potassium.

5.4 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participants will be documented (brand or generic name) and then updated at each visit on the specific visit CRF.

- Patients should not be treated with other ACE inhibitor or ARB while on study.
- Caution should be used when using nonsteroidal anti-inflammatory agents with Ramipril due to a potential decrease in renal function.
- Use of diuretics should be avoided, if possible while taking Ramipril because of the potential risk of dehydration
- Patients should avoid potassium supplements, if possible, while taking Ramipril because of the potential risk of hyperkalemia
- If the patient is taking potassium supplements and hyperkalemia is noted, potassium supplements should be discontinued and K+ re-checked within 24-72 hours before discontinuing study drug. The treating physician may hold the study drug until the lab is rechecked if he/she believes it is in the best interests of the patient.

5.5 Dose Modification

5.5.1 Radiation Therapy

Radiation delivery parameters are outlined in section 5.1.1.2. Dose modifications are not permitted however patients should be managed as per standard of care and evidence-based best clinical practice. Any treatment modifications made as a result must be recorded on the Ramipril Administration Form Week 6 (RT Completion).

5.5.2 Temozolomide

Temozolomide dose modifications should follow standard of care practices as outlined in the product monograph. All temozolomide treatment and dose modifications must be recorded on the Ramipril Administration Form Week 6 (RT Completion) and/or the Assessment Form in REDCap at all applicable visits after RT completion (*e.g.* Week 10, 14, 18, 22 and 26 visits).

5.5.3 Ramipril

If patient has been on Ramipril and develops toxicities after the titration period, the medication will be decreased to the next lower dose and maintained at that dose for the duration of the study. For example, 5 mg would become 2.5 mg. However, if the patient does not tolerate 2.5 mg they will stop study medication (Off Agent) and continue to be followed.

The threshold for dose modification will include the following:

- systolic blood pressure is less than 100 mm Hg,
- serum creatinine increases to above the upper limit of normal of either the local institutional lab or LabCorp (LabCorp normal creatinine value range is 0.76-1.27), or if the creatinine remains below the upper limit of normal but has increased >/= to 100% of the previous week's value from the same lab.
    - If an institutional creatinine result is used to guide Ramipril titration, then the upper limit of normal of the institutional lab should be used to guide titration

as described above.
    - Either the local institutional lab or LabCorp lab should be chosen and used for all Week 1-6 visits to be consistent with the normal values used during the titration period.
    - If choosing to use local institutional labs for Week 1-6 visits, please also draw and submit research LabCorp labs to allow for comparison across study sites.
- serum potassium rises above 5.0 mEq/L,
- Grade 3 or greater toxicity attributable to drug is identified during weekly toxicity evaluation.

Current Ramipril dose should be continued until the local institutional lab or research LabCorp lab results are received, which are used to evaluate these toxicities during Weeks 1-6 of RT (see Section 5.2 for further guidance). During Weeks 1-6 of RT, LabCorp labs and/or local institutional labs should be drawn only after ≥ 4 doses of current Ramipril dose have been taken by the patient. If local institutional labs are going to be used for toxicity assessments, please use them for all Week 1-6 visits for consistency and also draw research LabCorp labs to allow for comparison of labs across sites. At 1 month post-RT, standard of care local institutional labs will be used to evaluate toxicities per protocol. If a toxicity occurs that the treating physician feels requires a dosage medication that is not specifically list above, please notify the site coordinator and PI of the study.

In the event of inability to obtain LabCorp results in an appropriate time interval, local standard of care labs can be used for Ramipril titration decision making and other protocol related activities.
If lab abnormalities are detected that would affect the conduct of the study, treating physicians should consider whether correctable disease or treatment related toxicities (e.g. dehydration, nausea and vomiting, etc.) could be responsible. If so, clinicians should attempt to address those issues and repeat the labs within 24-48 hours for protocol decision making.

Refer to Section 8.3 for Off-Agent guidelines.

5.6 Adherence/Compliance

5.6.1 To be considered compliant with study medication, a participant must take at least 75% of scheduled doses. This determination will be done at the end of study by WF NCORP statisticians. Patients should be encouraged to remain on study and take the study medication even if they are known to be noncompliant with more than 25% of scheduled doses.

5.6.2 Compliance is monitored by daily diaries completed by the participant that are systematically collected weekly during radiation therapy and then monthly until 4 months post RT. In addition, compliance is monitored when appointments are made and when medication tolerance is assessed by the study team over the phone at week 14 and week 18. During the week 14 and 18 week phone contacts, participants should return study diaries via mail or in-person to the site study team. These data are entered into the study database for analyses by our biostatistician every 6 months when the study is reviewed by our DSMB.

6. PHARMACEUTICAL INFORMATION

6.1 Ramipril (IND-Exempt)

IND Status

The risks associated with Ramipril are not significantly increased in the proposed study population. The major risk of Ramipril in the non-hypertensive population is hypotension (11%). Ramipril has been used to treat several conditions in non-hypertensive patients including heart failure, post-myocardial infarction prophylaxis, and diabetic nephropathy and has been found to be safe in these settings. Furthermore, Ramipril is a generically available drug, and we are not conducting the proposed study in order to change the labelling instructions for Ramipril. A 10 mg dose of Ramipril was administered in 1,048 hypertensive and normotensive patients at risk of cardiovascular events and tolerability was generally considered to be good to excellent.[39] The HOPE study was a randomized trial of 10 mg dose of Ramipril vs placebo for cardioprevention in over 9500 patients in which 50% of the study population was normotensive at the beginning of the study.[40] A recent analysis of 160 patients treated with GBM at Wake Forest showed no difference in survival in patients treated with ACE inhibitors as compared to patients who were not treated with ACE inhibitors. As such, the risks associated with Ramipril are not significantly increased in the study population and therefore, an IND is not required.

6.2 Reported Adverse Events and Potential Risks

6.2.1 Patients Taking Ramipril for Hypertension

Altace® (Ramipril) has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in Altace® and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving Altace® in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in Altace® patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with Altace®. The most common reasons for discontinuation were cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

Of observed side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE® , only asthenia (fatigue) was more common on ALTACE® than placebo (2% vs 1%).

	Altace® **(n=651)**		**Placebo(n=286)**	
	n	%	n	%
Asthenia (Fatigue)	13	2	2	1

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the Ramipril group, not attributed at that time to Ramipril. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events might represent

Ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of Ramipril patients, with about 4% of these patients requiring discontinuation of treatment.

6.2.2 Patients Taking Ramipril for Heart Failure Post Myocardial Infarction

Adverse reactions (except laboratory abnormalities) considered possibly/probably related to study drug that occurred in more than one percent of patients and more frequently on Ramipril are shown below. The incidences represent the experiences from the AIRE study. The follow-up time was between 6 and 46 months for this study.

Percentage of Patients with Adverse Events Possibly/ Probably Related to Study Drug

Placebo-Controlled (AIRE) Mortality Study:

Adverse Event	**RAMIPRIL**	**PLACEBO**
	(N=1004)	**(N=982)**
Hypotension	11	5
Cough Increased	8	4
Dizziness	4	3
Angina Pectoris	3	2
Nausea	2	1
Postural Hypotension	2	1
Syncope	2	1
Vomiting	2	0.5
Vertigo	2	0.7
Abnormal Kidney Function	1	0.5
Diarrhea	1	0.4

HOPE Study:
Safety data in the HOPE trial were collected as reasons for discontinuation or temporary interruption of treatment. The incidence of cough was similar to that seen in the AIRE trial. The rate of angioedema was the same as in previous clinical trials (see WARNINGS in the package insert).

	RAMIPRIL(N=4645)	**PLACEBO(N=4652)**
	%	%
Discontinuation at any time	34	32
Permanent discontinuation	29	28
Reasons for stopping Cough	7	2
Hypotension or Dizziness	1.9	1.5
Angioedema	0.3	0.1

Other adverse experiences reported in controlled clinical trials (in less than 1% of Ramipril patients), or rarer events seen in post-marketing experience, include the following (in some, a causal relationship to drug use is uncertain):
Body As a Whole: Anaphylactic reactions. (See WARNINGS in the package insert.)

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (See WARNINGS and PRECAUTIONS in the package insert), syncope and palpitations.

Hematologic: Pancytopenia, hemolytic anemia and thrombocytopenia.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE®, particularly when ALTACE® was given concomitantly with a diuretic. (See WARNINGS in package insert.) Acute renal failure.

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS in package insert.)

Gastrointestinal: Hepatic failure, hepatitis, jaundice, pancreatitis, abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, increased salivation and taste disturbance.

Dermatologic: Apparent hypersensitivity reactions (manifested by urticaria, pruritus, or rash, with or without fever), photosensitivity, purpura, onycholysis, pemphigus, pemphigoid, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Miscellaneous: As with other ACE inhibitors, a symptom complex has been reported which may include a positive ANA, an elevated erythrocyte sedimentation rate, arthralgia/arthritis, myalgia, fever, vasculitis, eosinophilia, photosensitivity, rash and other dermatologic manifestations. Additionally, as with other ACE inhibitors, eosinophilic pneumonitis has been reported.

Fetal/Neonatal Morbidity and Mortality. See WARNINGS in package insert**:** Fetal/Neonatal Morbidity and Mortality.

Other: Arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Post-Marketing Experience: In addition to adverse events reported from clinical trials, there have been rare reports of hypoglycemia reported during ALTACE® therapy when given to patients concomitantly taking oral hypoglycemic agents or insulin. The causal relationship is unknown.

Clinical Laboratory Test Findings

Creatinine and Blood Urea Nitrogen: Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE® alone, and in 1.5% of patients receiving ALTACE® and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE® alone and in 3% of patients receiving ALTACE® with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See WARNINGS and PRECAUTIONS in package insert.) Since Ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See WARNINGS and PRECAUTIONS in package insert.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dL or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE® alone and in 1.5% of patients receiving ALTACE® plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE® administration. Elevations of liver enzymes, serum bilirubin uric acid, and blood glucose have been reported, as have cases of hyponatremia and scattered

incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

6.3 Availability

Ramipril is available for oral administration in 1.25, 2.5, 5, and 10 mg capsules. The drug will be obtained, packaged, and distributed by McKesson Corporation (Winston-Salem, NC). McKesson Corp. will also provide storage and inventory for the study drug. Ramipril will be provided to study participants in 1.25 mg capsules at no cost. The Wake Forest NCORP Research Base will be providing all funding for Ramipril.

6.4 Agent Distribution

Ramipril will be distributed by McKesson, Corp. Winston-Salem, NC (1-800-693-4906; fax: 1-919-256-0794). McKesson, Corp. will distribute Ramipril directly to participating sites following enrollment of study patients. Ramipril will be provided to participants at no cost.

6.5 Agent Accountability

The Site Investigator, or a responsible party designated by the Site Investigator, must maintain a careful record of the inventory and disposition of all agents received from McKesson using the NCI Drug Accountability Record Form (DARF) which can be found using the following link https://ctep.cancer.gov/forms/docs/agent_accountability.pdf. The Site Investigator is required to maintain adequate records of receipt, dispensing and final disposition of study agent. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

6.6 Packaging and Labeling

When a patient is enrolled to the study, local NCORP site should complete a Drug Order Request Form located in REDCap and fax to McKesson Corporation. Upon receipt of the request form, McKesson Corp. will confirm your site is approved for the study and will ship the drug to the local NCORP site. McKesson Corp. will call the local NCORP site Study Contact person to confirm the order was received. They will require the following information from the site:

- Patient Full Name or Initials
- Site Shipping Address and phone number
- Doctor's name

For all drug shipments from McKesson Corp., a packing slip will be enclosed that includes the date and quantity of drug provided, patient name/initials, study ID number, drug identification including lot number and expiration date.

All drug orders are shipped Priority Overnight delivery in a box designed to maintain temperature stability.

Once study drug is received at the local NCORP site, the designated site coordinator validates that the contents of the package (study medication received) matches the information provided on the packing slip. The inventory and disposition of Ramipril pills must be recorded using the NCI Drug Accountability Record Form (DARF). See section 6.5 Agent Accountability.

The first shipment of Ramipril per patient will contain a single bottle of 133 capsules. This shipment will provide the patient with drug through the first 6 weeks of treatment (Week 1-6 of RT). Prior to the completion of the first 6 weeks of treatment, McKesson Corp. will confirm the patient needs additional study drug, before shipping it to the local NCORP site. This second patient-specific shipment will contain a maximum of four bottles of Ramipril, containing 112 (1.25 mg) capsules each. This second shipment will last the patient for the final 4 months of Ramipril treatment, through Week 22 (4 Month Post-RT.

6.7 Storage

Ramipril should be stored at room temperature per package insert.

6.8 Agent Destruction/Disposal

Participating sites will dispose of unused portions of Ramipril according to their institution's SOPs.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Schedule of Events(A)

Evaluation/ Procedure	Enrollment	Baseline (B)	Titration of drug during RT (Wk 1-3)	During RT (Wk 4-5)	RT Completion (Wk 6)	1-month post RT (Wk 10)	2- & 3-Month post RT (Wk 14, 18) Phone Call	4-month post RT (Wk 22)	5- month post RT Wk 26) Phone Call
Eligibility/Enrollment	X								
Patient Demographics	X								
Medical History (1)		X				X		X	
Concurrent Medications & Supplements		X	X	X	X	X	X	X	X
Physical Exam (1)		X				X		X	
Blood Pressure		X	X	X	X	X		X	
Comprehensive Metabolic Panel (D)		X	X	X	X	X			
ECOG Performance Status		X							
Serum or Urine βHCG (2)		X							
ApoE Genotype (C)		X							
MRI/CT Brain (3)		X				X		X	
Toxicity Assessment			X	X	X	X			
Adverse Event Reporting			X	X	X	X	X	X	X
Medication Diary		X	X	X	X	X	X	X	
Pill count (Unused Study Agent)					X	X		X	
Ramipril Administration			X	X	X	X	X		
TTFields or Optune® Device						X	X	X	
Chemoradiation Summary					X				
Off Agent (E)			----------Only if applicable ----------						X
Off Study (F)			----------Only if applicable ----------						X
Cognitive & PRO Testing									
HVLT-R		X			X	X		X	
Trail Making Test, Part A		X			X	X		X	
Trail Making Test, Part B		X			X	X		X	
COWAT		X			X	X		X	
EORTCLQ-30/BN20		X			X	X		X	
Shipley Institutional of Living Scale		X							

(A) Refer to Section 7.3 for details of each evaluation or procedure

(B) Baseline evaluations and labs are required within 14 days of enrollment, excluding MRI. (Section 4.1.7).

(C) Research test only; refer to Section 9.0 for details.

(D) Inclusive of creatinine, potassium, GFR, Total Bilirubin, AST and ALT. It should be noted that CMPs on Week 1, 2, 3, 4, 5, & 6 during RT should be drawn only after ≥ 4 doses of current Ramipril dose has been taken by the patient. CMPs should be analyzed through LabCorp and paid by the study directly to LabCorp. If sites chose to use CMPs from local institutional labs for toxicity assessments, LabCorp CMPs should still be drawn. Sites should keep the same lab for toxicity assessments for all Week 1-6 labs for each patient. At Baseline and 1 month post-RT standard of care local labs will be used for the study.

(E) All study assessments should still be completed, unless patient is unwilling or withdraws consent.

(F) If the patient is going Off Study, complete all forms for the current visit, as well.

(1) Can be obtained ≤ 14 days prior to enrollment

(2) Negative serum or urine pregnancy test required within 14 days prior to enrollment for women of childbearing potential. Results may be used from routine local lab.
(3) MRI/CT Brain scans at the indicated time points are considered standard of care per national guidelines. As per section 4.1.7, all available brain MRI or CT imaging reports from surgery to study completion must be submitted. This includes any post-operative or pre-radiation scan reports. Treating physician assessment of tumor response – i.e. response, progression or stable disease – will be captured for each completed imaging study.

Notes:

- If RT is delayed, Ramipril will still be given and continue to be given until 4-months Post RT (Week 22). That is, the visits will be pushed out the length of the delay.
- If a patient decides to discontinue participation in study at any time prior to study completion, the entire battery of neurocognitive (except Shipley) and participant related outcomes tests and forms should be administered. (Refer to Section 8.3 for Off-Study Details)

7.2 Study Visit Windows

Study Visit	Visit Window
Enrollment	n/a
Baseline	≤ 14 days after Enrollment
Titration of Drug (Week 1-3)	+/- 3 days
During RT (Week 4-5)	+/- 3 days
RT Completion (Week 6)	+/- 3 days
1-month Post RT (Week 10)	+/- 7 days
2- & 3- month post RT (Week 14 & 18) Phone calls	+/- 7 days
4- month post RT (Week 22)	+/- 7 days
5- month post RT (Week 26) Phone Call	+/- 7 days

7.3 Evaluations and Procedures

Eligibility/Enrollment: Patient must sign the IRB approved study informed consent before any study-related evaluations or procedures are complete. Then, study team should complete the Enrollment Checklist to determine if a patient is eligible for the study before they are enrolled. Patients should be enrolled electronically as described in Section 13.3.

Patient Demographics: Patients should complete the Patient Demographic and Health Related Behaviors Form at Enrollment.

Medical History: Medical History should be performed within 14 days prior to enrollment. This Medical History should be reviewed and updated at the following 2 visits: Months 1- and 4- post RT. Forms for each visit have required data collected.

Concurrent Medication & Supplements: Current medications should be compiled at Baseline and then updated at each study visit throughout RT. Patients should be seen by the study team at the 1- and 4-month post RT visit to update changes in medication. Patients should be called at 2- and 3- month post RT visits to determine any updates.

Physical Exam: Exams should be performed by MD, NP or PA within 14 days prior to enrollment. They should also be performed at the following 2 visits: Months 1- and 4- post RT. Forms for each visit have required data to be collected.

Blood Pressure: Blood pressure should be recorded and reviewed for any Dose Modifications (see Section 5.6) at Baseline, each week during RT (Wk 1-6) and at the following 2 visits: Months 1- and 4- post RT. Refer to Section 5.5 for criteria for Dose Modifications.

Comprehensive Metabolic Panel (CMP): Inclusive of creatinine, potassium, GFR, Total Bilirubin, AST and ALT. Labs are required within 14 days of enrollment. These labs should also be collected at Baseline, Weeks 1-6 during RT and at 1 Month Post RT (Wk 10). Refer to Section 5.5 for criteria for Dose Modifications related to labs. The CMPs for Week 1, 2, 3, 4, 5 & 6 during RT should be analyzed through LabCorp and paid by the study directly to LabCorp. If local sites perform CMPs at Week 1, 2, 3, 4, 5 or 6 during RT as standard of care, these values can be used to determine toxicity, but LabCorp CMPs should also be drawn for consistence across study sites. Sites should choose if LabCorp or local institutional lab values will be used to assess drug related toxicity that determines if dose escalation per protocol is appropriate during weeks 1-6 of RT. The same lab should perform the CMPs for Week 1-6 visits. At Baseline and 1 month post RT, standard of care local labs should be used for the study and to determine toxicity, if applicable.

In the event of inability to obtain LabCorp results in an appropriate time interval, local standard of care labs can be used for Ramipril titration decision making and other protocol related activities.

If lab abnormalities are detected that would affect the conduct of the study, treating physicians should consider whether correctable disease or treatment related toxicities (e.g. dehydration, nausea and vomiting, etc.) could be responsible. If so, clinicians should attempt to address those issues and repeat the labs within 24-48 hours for protocol decision making.

ECOG (Eastern Cooperative Oncology Group) Performance Status: Study Team should determine the patient's ECOG performance status using the chart in Appendix A at the Baseline visit.

Serum or Urine βHCG: A negative serum or urine pregnancy test is required within 14 days prior to enrollment for women of childbearing potential. Results will be used from standard of care local labs.

APOE Genotyping: At Baseline, a blood vial of approximately 8 ml will be taken from a vein in the arm/central line for lab analysis. Blood samples will be stored with a unique identifier and will not include any information protected by HIPAA regulations. Blood samples will be stored at Wake Forest. See Section 9.0 for specimen management.

MRI/CT Brain: MRI Brain will be completed per standard of care at each study site. Sites are asked to provide MRI final reports with the specific visit form. As per section 4.1.7, patients who are unable to undergo MRI scanning should have CT brain scans done as per this schedule. Treating physician assessment of tumor response – i.e. response, progression or stable disease – will be captured for each completed imaging study.

Toxicity Assessments: Assessments by the study team will be done from Week 1 of RT and the start of Ramipril to 5-month post RT (end of study). This time period includes 30 days after treatment with Ramipril. Refer to section 6.2 for reported adverse events and risks when taking Ramipril.

Adverse Event Reporting: Refer to Section 10 of the protocol for specifics.

Medication Diary: Each patient is asked to fill in a Ramipril Medication diary and return it to the study team weekly during radiation therapy (weeks 1-6), and monthly on 1- and 4- month post RT visit. Since 2- and 3- month visits can be phone calls, the patient will need to mail back these diaries to the study team. Refer to Appendix D for a Ramipril Medication diary.

Pill Count: Patients will be asked to bring pill bottles to visit. Study team will count and record pills given, remaining and taken on the visit CRF.

Ramipril Administration: This study drug will be provided at no charge to patients for oral administration daily from Week 1 RT to post 4-month RT (Week 22). Study team will be required to order, distribute and inventory study drug. Refer to Sections 6.3 – 6.8 and for titration schedule 5.1.2 for details.

Chemoradiation Summary: At the RT Completion (Week 6) visit, a summary of the standard of care chemotherapy and radiation therapy will be gathered.

Off Agent: Use this form when a patient goes Off Agent either at the completion of study drug administration per protocol or at the time of early discontinuation. All study assessment should be continue to be completed, unless the patient is unwilling or withdraws consent. LabCorp samples do not need to be collected after the patient is Off Agent. Please use local labs to complete assessment information in REDCap.

Off Study: Use this form when a patient goes Off Study by either withdrawing consent or completing the study. This form serves as a way to track the patient status.

Cognitive & PRO Testing:

Participant Related Outcomes Assessments (PRO) (EORTCLQ-30/BN20): Study Team should administer at Baseline, RT Completion, 1- and 4- month post RT visits. *If patient goes Off-Study for any reason, the PRO should be administered.*

Neurocognitive Assessments (HVLT-R, Trail Making Tests, Part A & B, COWAT and Shipley Institute of Living Scale): The entire battery of neurocognitive tests and questionnaires will be administered by a trained and certified examiner. Refer to Section 7.6 for specifics. Note that the Shipley Institute of Living Scale will only be given at Baseline, while all others are also given at RT Completion, 1- and 4- Post RT visits. *If patient goes Off-Study for any reason, the entire next set of Neurocognitive Assessments should be administered, except the Shipley Institute of Living Scale.*

7.4 Study Agent - Ramipril

Study agent Ramipril will be given from Week 1 of RT until 4 months post RT (Week 22). A titration period will be during weeks 1-3 of RT to determine the maximum dose, which will be continued until 4 months post RT (Week 22).

Refer to the following sections for details as needed:

- Section 5.1 Dose Regimen
- Section 5.2 Administration, including titration period
- Section 5.3 Contraindications
- Section 5.4 Concomitant Medications
- Section 5.5 Dose Modifications

- Section 5.6 Adherence/Compliance

7.5 Evaluation at Completion of Study Intervention

The study agent Ramipril will be discontinued at 4 months post radiation therapy or, prematurely, if any of the Off-Agent criteria are met (refer to section 8.3). At this visit the study team should complete the Off Agent form and any other forms required for the visit.

7.6 Methods for Neurocognitive & Participant Related Outcomes Tests

7.6.1 Specific Training and Certification Procedures

Each participating site will be required to have at least one examiner who is trained and certified in the administration and scoring of the cognitive battery (neurocognitive tests and questionnaires). Training will follow the procedures developed in prior WF NCORP neurocognitive studies such as our recently completed Phase II feasibility study trial of donepezil in breast cancer survivors previously exposed to chemotherapy. We will train using didactic presentations (describing the purpose and instructions for each test and questionnaire), live and video demonstrations of a complete battery administration, live practice sessions supervised by a certified examiner and trainer with specific feedback, and a review by certified trainers of an audio-recorded administration. If needed, remediation will occur with review of subsequent recorded administrations with corrective feedback. Once the examiner has met study criteria s/he will be certified to administer and score the battery at his/her site. Periodic re-certifications will be required. If an examiner has been trained and certified previously by WF NCORP RB and has administered <u>all</u> of the neurocognitive tests required in this protocol within the last 12 months, they will only need to participate in an abbreviated training. This procedure has been successfully used in our studies of cognitive effects of cancer and its treatments as well as by Dr. Rapp and his team in large scale, multi-site clinical trials and observational studies (e.g., WHIMS, CoSTAR, SPRINT, Look AHEAD, LIFE, MESA).

7.6.2 Participant Reported Outcomes (PRO) Assessment
(Translations Not Available; enrollment restricted to English-speaking participants)

<u>EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ-30/BN20)</u>
The EORTC QLQ-C30/BN20 were developed and validated for use in this patient population. The QLQ-C30 is a 30-item self-report questionnaire that has patients rate the 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 BN20 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.[41]

7.6.3 Neurocognitive Function Assessments
(Translations Not Available; enrollment restricted to English-speaking participants)

The healthcare professional who is responsible for test administration in this study must be pre-certified by WF NCORP Site Coordinator for each test, unless they are currently certified with WF NCORP for each test. Refer to Section 7.6.1.

The tests in the neurocognitive test battery were selected because they are widely used standardized psychometric instruments that have been shown to be sensitive to the impact of cancer and the neurotoxic effects of cancer treatment in other clinical trials.[42] The tests have published normative data that takes into account age, and where appropriate, education and gender. The tests are given by certified site administrators, and the total time for the cognitive assessment is approximately 38 minutes, as follows:

Cognitive Domain	**Test**	**Administration Time** (minutes)
Memory	Hopkins Verbal Learning Test-Revised (HVLT-R)	5
Cognitive Processing Speed	Trail Making Test, Part A	3
Executive Function	Trail Making Test, Part B	5
Verbal fluency	Controlled Oral Word Association Test (COWAT)	5
Cognitive Reserve	Shipley Institute of Living Scale	20

Hopkins Verbal Learning Test-Revised (HVLT-R)
The patient is asked to recall a list of 12 words over three trials. After a delay of 20 minutes, the patient is asked to spontaneously recall the words. The patient is then asked to identify the list words from distractors. There are six alternate forms of this test to minimize practice effects. The test measures learning memory retrieval, and memory consolidation processes. This measure has been widely used in clinical trials.[43]

Trail Making Test, Part A
This is a test of visual-motor cognitive processing speed, requiring the patient to connect dots in numerical order from 1 to 25 as fast as possible.[44]

Trail Making Test, Part B
This test is similar to Trail Making Test Part A, with the additional requirement of shifting mental set (an executive function). The patient connects dots alternating numbers and letters as fast as possible.[41]

Controlled Oral Word Association Test (COWAT)
This is a test of phonemic verbal fluency. The patient is asked to produce as many words as possible in 60 seconds beginning with a specified letter. There are two alternate forms of this test .[45]

Shipley Institute of Living Scale-Version 2 Vocabulary
This vocabulary test requires respondents to read a target word and select one of four words that most closely means the same thing. Score it total correct of 40 items. This provides an assessment of premorbid intellectual functioning comparable to a verbal IQ and thus is a proxy for cognitive reserve. It will be administered only at baseline.[46]

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Primary Endpoints

Retention rate at 10 weeks of treatment (6 weeks during RT and 4 weeks [1 month] post RT): Retention will be defined as compliance with drug therapy for at least 75% of doses during the 10 week treatment and completion of the composite neurocognitive battery as detailed below.

Neurocognitive performance measured by the Clinical Trial Battery Composite (CTB COMP) score at 10 weeks of treatment (6 weeks during RT and 4 week [1 month] post RT): Tests have been selected to represent a range of functions affected by cancer and RT including attention, memory, working memory, executive functions and verbal fluency. All cognitive testing will be performed by trained and certified research staff. Proposed neurocognitive measures are: Hopkins Verbal Learning Test-Revised (HVLT-R Delayed Recall; 5 min);[47,48] Trail Making Test A & B (TMT; 8 min) [49] and Controlled Oral Word Association test (COWAT 3 letters; 5 min).[50] The composite neurocognitive score is defined as the arithmetic mean of the standardized scores from the HVLT-R total recall, HVLT-R Delayed Recall, HVLT-R Delayed Recognition Discriminability (all portions of the HVLT-R delayed recall), Trail Making Test Part A, Trail Making Test Part B, and COWAT.[51] We will assess the effect size in terms of the composite neurocognitive score.

The entire battery of neurocognitive tests and questionnaires will take approximately 38 minutes to complete. We have used a similar battery successfully in two phase 2 studies and one phase 3 study involving breast and brain tumor cancer survivors. Data completeness in those studies was over 95%.

8.2 Secondary Endpoints

Participant reported outcomes (PRO): Participant-reported outcomes will complement the neurocognitive battery. The EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/BN20) will measure several domains of functioning (physical, emotional, cognitive, social, fatigue, pain, etc.) (8 minutes).[52] Each cognitive test and PRO proposed has adequate psychometric properties and has been used previously in clinical trials of oncology patients[52].

Imaging: Adequate imaging for diagnostic, treatment planning and follow-up imaging will follow standard of care practices and will include contrast-enhanced T1-weighted MRI and T2 or FLAIR imaging. Contrast-enhanced CT will be allowed only in cases where patients are unable to undergo MRI because of non-compatible devices. MRI of the brain will be performed 1- and 4-month post-RT or until time of tumor progression, should that occur prior to the 4-month post-RT time point. Response assessment will be based on treating investigator assessment and institutional standard of care. Imaging parameters will only be utilized to measure response and progression.

Other variables to be measured: Sociodemographic variables to be assessed in a questionnaire at baseline will include age, education, race/ethnicity, menopausal status, co-morbid medical conditions, concomitant medication, marital status, socioeconomic status, tumor size and location. Variables to be assessed after completion of each treatment phase by treating physician include dates, dose and compliance of temozolomide administration, radiation dose, radiation dose per fraction, and radiation volume (e.g. planned treatment volume (PTV)). *Cognitive reserve* (CR) will be measured with the Shipley Scale-Vocabulary with educational (years in school) and occupational attainment (standardized 8-level classification) also measured as proxies for CR.

Biomarkers: APOE genotype, a risk factor for cognitive impairment and dementia, will be derived from

whole blood samples taken at baseline at the site of study enrollment. See Section 10.1 for sampling handling and processing.

8.3 Off-Agent/Off-Study

Each participant has the right to withdraw from treatment or from the study at any time without prejudice.

8.3.1 Off-Agent Criteria

Participants may stop taking study agent for one or more of the following reasons: completed the protocol-prescribed intervention, adverse event (AE) or serious adverse event (SAE), inadequate agent supply, refusal to continue with study procedures, the need for contraindicated concomitant medications, medical contraindication, disease progression, death or treating physician decision.

Date and reason off-agent should be documented on the Off Agent case report form. Reasons that are not specified on the form should be coded as 'Other' and a brief description provided. Patients who go off-agent must be followed for adverse events (AEs) for at least 30 days from their last treatment.

Note that participants who go off-agent should be encouraged to stay in the study and provide data at the regularly scheduled visits. Local NCORP site staff should complete the study assessment with the patient, especially the neurocognitive and PROs testing and toxicity assessments. LabCorp samples do not need to be collected once the patient is "Off Agent.". Local institutional labs can be used to assess the participant after they are off Ramipril.

8.3.2 Off-Study Criteria

Participants may go 'off-study' for one or more of the following reasons: the protocol intervention and any protocol-required follow-up period is completed, AE/SAE, lost to follow-up, refusal to continue with study procedures, the need for contraindicated concomitant medication, medical contraindication, disease progression, withdraw consent, death, determination of ineligibility (including screen failure), pregnancy, or treating physician decision.

Note that a participant is not automatically taken off-study if they refuse further treatment. In fact, these participants should be encouraged to remain in the study and provide data at their regularly scheduled visits. Date and reason off-study should be documented on the Off Study case report form. Reasons that are not specified on the form should be coded as 'Other' and a brief description provided.

A final evaluation of the participant should be performed when he/she withdraws from the study. If a patient decides to discontinue participation in study at any time prior to study completion, the entire battery of neurocognitive tests and forms should be administered, using the next Neurocognitive and PRO booklet they would have received as well as, all other items in the Schedule of Events (Section 7.1) for the visit.

8.4 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9.0 SPECIMEN MANAGEMENT

A single blood draw will be made at the baseline visit. DNA will be isolated from whole blood for APOE genotyping, collected in one (8 ml max) yellow-top Vacutainer tubes (with citrate as the preservative). Samples will be sent to WFUHS for storage and processing.

9.1 Sample Processing

Blood samples received from all sites will be brought to the Wake Forest Center for Genomics and Personalized Medicine Research laboratories, where they will be entered into a database and the DNA isolated. DNA from whole blood will be isolated using the AutoPure LS instrument (Qiagen, Inc.).

SNP genotyping of the APOE haplotype will be performed in the Center for Genomics and Personalized Medicine Research at Wake Forest using the iPlex SNP genotyping system (Sequenom, Inc.), which has been successfully tested and fully integrated into our laboratory. The APOE haplotype will be determined by genotyping the two individual SNPs that make up the haplotype, rs429358 and rs7412, in each individual. Genotypes will be scored using the SpectroTyper software (Sequenom, Inc.), and quality control parameters (e.g., CEPH DNA samples, negative controls) will be determined. Problem samples or SNPs will be reviewed and repeated if necessary.

9.2 Site Collection and Handling Procedures

APOE genotype will be derived from approximately 8 ml of whole blood sample taken from a vein in the arm/central line at baseline, at each NCORP site of study enrollment. Prepared shipping kits will be sent to participating NCORP sites from the Wake Forest Biotech Laboratory, who will provide sample handling, storage, tracking, and logistics.

9.3 Shipping Instructions

Initial Shipping Kits:
Sites should request shipping kits at the time of study approval in advance of putting patients on study and should use the Specimen Kit Request Form (Appendix E). This form should be emailed (NCORP@wakehealth.edu) or faxed to Wake Forest NCORP Research Base at (336) 716-6275.

Additional Shipping Kits:
If additional kits are needed, sites should email the Specimen Kit Request Form directly to the Wake Forest NCORP Biospecimen Laboratory using their email (7NCORP@wakehealth.edu). For additional details refer to Appendix E.

10.0 ADVERSE EVENTS REPORT REQUIREMENTS

DEFINITION: Adverse event (AE) refers to any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are generally considered AEs, and may need to be reported as per

instructions in Section 10.3 below. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) generally not reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur can be found in Section 6.2 Reported Adverse Events and Potential Risks, as well as the manufacturer's package insert.

10.1 Adverse Events (AEs)

10.1.1 Reportable AEs

Following the guidance in Section 10.3, any reportable AEs that occur after the informed consent is signed and baseline assessments are completed should be recorded on the REDCap AE CRF whether or not related to study agent, as detailed below.

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations

10.1.2 AE Data Elements

The following data elements are required for AE reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a SAE
- Whether or not the subject dropped due to the event
- Outcome of the event

10.1.3 CTCAE term (AE description) and Grade

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Identify the AE using the CTCAE version 5.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v5.0. as stated below.

CTCAE v5.0 general severity guidelines:

GRADE	SEVERITY	DESCRIPTION
1	**Mild**	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	**Moderate**	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).*
3	**Severe**	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.**
4	**Life-threatening**	Life-threatening consequences; urgent intervention indicated.
5	**Fatal**	Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.1.4 Assessment of Relationship of AE to Treatment

The possibility that the AE is related to study agent will be classified as one of the following attribution: Unrelated, Unlikely, Possible, Probable, Definite.

Attribution: An assessment of the relationship between the adverse event and study agent/intervention, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is clearly NOT related to the study agent (or product)/intervention
Unlikely	The AE is doubtfully related to study agent /intervention
Possible	The AE may be related to study agent/intervention
Probable	The AE is likely related to study agent/intervention
Definite	The AE is clearly related to study agent/intervention

10.1.5 Follow-up of AEs

Any reportable AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such.

10.2 Serious Adverse Events (SAEs) [Reporting Overview]

DEFINITION: Serious Adverse Event (SAE) is defined by regulation 21 CFR §312.32 as any adverse

medical event (experience) that results in at least one of the outcomes listed below:

- Death
- Life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

Hospitalization (or prolongation of hospitalization): For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.

10.3 Reporting of Adverse Events (AEs) for WF-1801

Any reportable adverse event, as defined below, whether observed by study staff or investigator, elicited from or volunteered by the participant, should be documented. Each reportable adverse event will include the date of onset, date of resolution, severity, and the relationship to the study agent or intervention, and any action taken with respect to the study agent or intervention. Please review the chart and instructions below to determine, which AEs are reported for WF-1801.

Reasons for Not Reporting All Adverse Events

- Ramipril is a widely used medication taken routinely for high blood pressure on an outpatient basis. Side effects are well documented.

- Because Ramipril is widely used and its toxicity profile is well established, we feel the likelihood of Ramipril increasing standard treatment-related toxicities is low. By not collecting all AEs, we hope to expend our efforts in identifying toxicities that are unexpected and related to Ramipril.

Adverse Events (AEs) to be reported for WF-1801

- **Grade 3:** Any **unexpected** adverse events (AEs) **grade 3** that have an attribution to the intervention of **Possible, Probable or Definite** should be reported.

- **Grade 4:** Any **unexpected** adverse events (AEs) **grade 4** should be reported.

- **Grade 5:** All adverse events (AEs) **grade 5** should be reported.

Methods and Timing of Reporting Adverse Events

Please refer to the chart below for method(s) of reporting.

- **All reportable adverse events** will be reported to the Wake Forest NCORP Research Base using REDCap Adverse Event Reporting.

- **Non-expedited Reporting:** Adverse events not requiring expedited reporting through CTEP-AERS should be entered into REDCap within 10 calendar days of learning of the event.

- **Expedited Reporting:** See Section 10.4 for CTEP-AERS expedited reporting.

- Site staff and/or Principal Investigators will also notify WF NCORP Research Base via REDCap reporting and report to CTEP-AERS within 24 hours of discovering the details of all **unexpected (possible, probable and definite) severe, life-threatening (grade 4) and all (expected or unexpected) fatal adverse events (grade 5).**

- All recorded adverse events reported to the Wake Forest NCORP Research Base will be reviewed by the Wake Forest NCORP Research Base Data and Safety Monitoring Committee (DSMC) and will be included in statistical reports to the Wake Forest NCORP Research Base Data and Safety Monitoring Board (DSMB).

Adverse Events								
	Grade 1 & 2		**Grade 3**		**Grade 4**		**Grade 5**	
	Expected	**Unexpected**	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected**	**Unexpected**
Unrelated						REDCap	REDCap & CTEP-AERS	REDCap & CTEP-AERS
Unlikely						REDCap	REDCap & CTEP-AERS	REDCap & CTEP-AERS
Possible				REDCap		REDCap & CTEP-AERS	REDCap & CTEP-AERS	REDCap & CTEP-AERS
Probable				REDCap		REDCap & CTEP-AERS	REDCap & CTEP-AERS	REDCap & CTEP-AERS
Definite				REDCap		REDCap & CTEP-AERS	REDCap & CTEP-AERS	REDCap & CTEP-AERS

The Wake Forest NCORP Research Base Multi-PI(s), the Wake Forest NCORP Research Base DSMC and/or Study Chair will take appropriate action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.

Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All CTEP-AERS reports should be sent to the local IRB in accordance with the local IRB policies.

10.4 Responsibilities of Local Sites for Expedited Reporting (CTEP-AERS)

Wake Forest NCORP affiliates and sub-affiliates (local sites) are required to notify the WF NCORP Research Base if a participant has an adverse event requiring expedited reporting by emailing NCORP@wakehealth.edu. All SAEs that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site, https://ctepcore.nci.nih.gov/ctepaers/security/login.

IMPORTANT: When reporting in CTEP-AERS please ensure a copy of the report is sent to WF NCORP RB by adding NCORP@wakehealth.edu to the distribution list within the reporting system.

Any correspondence between CTEP-AERS and/or the FDA about a reportable SAE should be forwarded to NCORP@wakehealth.edu also.

Commercial reporting requirements are provided in the table below. The commercial agent used in this study is Ramipril (Altace®).

Expedited reporting requirements for adverse events experienced by participants who are receiving study agent/intervention (including within 30 days of the last administration of commercial study agent/intervention) should be reported as follows:

Attribution	Grade 4		Grade 5	
	Expected	Unexpected	Expected	Unexpected
Unrelated or Unlikely			CTEP-AERS	CTEP-AERS
Possible, Probable, Definite		CTEP-AERS	CTEP-AERS	CTEP-AERS

1) This includes all deaths within 30 days of the last dose of study agent with a commercial agent/intervention, regardless of attribution. Any death that occurs more than 30 days after the last dose of study commercial agent/intervention and is attributed (possibly, probably or definitely) to the agent/intervention and is not due to cancer recurrence must be reported according to the instructions above.

2) Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the CTEP-AERS, CIRB or WF NCORP RB in order to complete the evaluation of the event.

For more information see:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

Contact Information for NCI Safety Reporting:

CTEP-AERS Website (for submitting expedited reports)	https://ctepcore.nci.nih.gov/ctepaers/security/login
CTEP-AERS Medical Questions	aemd@tech-res.com 301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM ET
CTEP-AERS Technical Help	1-888-283-7457 ncictephelp@ctep.nci.nih.gov
CTCAE Help/Questions	https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm ncicctcaehelp@mail.nih.gov

CTEP-AERS FAQs	https://ctepcore.nci.nih.gov/ctepaers/help/webhelp/welcome/help%20-%20frequently%20asked%20questions.htm
CTEP-AERS Training	https://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

11. STUDY MONITORING

11.1 Data Management

Data management for this study will be done electronically using the following systems.

Informed consent document	REDCap
Protocol registration form	OPEN/REDCap
Surveys and Data Collection Forms	REDCap

REDCap is a secure, web-based, and easy to program forms and research database platform utilized by the WF NCORP for many research projects. This study will be using REDCap as the electronic data collection platform with electronic Case Report Form (eCRF) for multi-site studies.

11.2 Case Report Forms

Protocol-specific case report forms (CRFs) will be submitted electronically to the WF NCORP Research Base Data Management Center via REDCap. Refer to Appendix B for a data submission checklist, showing the specific forms that are needed for each study visit.

Do not submit study data or forms to CTSU Data Operations.
Do not copy the CTSU on data submissions.

11.3 Source Documents

Source documents are the original signed and dated records of participant information (e.g., the medical record, shadow chart) which may include electronic documents containing all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs.

- Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

All laboratory reports, pathology reports, x-rays, imaging study and scans must have:

- Complete identifying information (name and address of the organization performing, analyzing, and/or reporting the results of the test); and
- Range of normal values for each result listed.

11.4 Data and Safety Monitoring Plan

In accordance with the NIH requirement, a Data Safety and Monitoring Plan (DSMP) has been established to guide the oversight of this study in order to ensure the safety of participants and the validity and integrity of the data. This monitoring will be commensurate with minimal risk present to participants.

The Wake Forest NCORP Research Base Data and Safety Monitoring Committee (DSMC) meets monthly to review reportable Adverse Events and Protocol Deviations to identify urgent safety and data concerns that may affect study safety and data quality. Adverse Event and Protocol Deviation reports are generated by the Wake Forest NCORP Research Base Data Management team. The DSMC consists of members of the Wake Forest NCORP Research Base team including one of the NCORP Research Base Multi-PIs, the Wake Forest NCORP Research Base Administrator, regulatory, and data team members.

The Wake Forest NCORP Research Base Data and Safety Monitoring Board meets every six months to review Wake Forest NCORP Research Base protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences, biostatistics and ethics. The DSMB report is generated by the Research Base statistician. Areas of review may include the following: Study Objectives; Patient Accrual; Patient Status and Retention; Study Status; Last Contact Status; Patient Compliance; Number of Biopsies/Labs as needed; Patient Characteristics; Summary of Observed Toxicities; Adverse Events; Date, Event briefly described, Relationship to Drug, Arm assigned; Summary of Primary and Secondary Measures.

DSMB Responsibilities: The DSMB reviews accrual information and interim analyses of outcome data and cumulative toxicity data summaries to determine whether:

- the trial should continue as originally designed
- the trial should be changed
- the trial should be terminated
- outcome results should be released prior to the reporting of the study results

Members of this committee as well as the organization statistician will oversee the safety monitoring of the study to ensure that the privacy of all participants in the study is protected; ensure that participants' interests are primary, that is, above the interests of the scientific investigation; and to ensure that all data collection is scrutinized for accuracy, privacy and levels of protection. The committee will perform reviews of the data handling and confidentiality and comply with recommendations to resolve such problems, and maintain written communication of the deliberations and recommendations that arise from their meetings. By examining this information, they will keep abreast of critical issues regarding recruitment and data integrity. Reports of all DSMB meetings and recommendations will be provided to the NCI, CIRB, WF NCORP RB, and participating sites, as requested.

11.5 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Study PI and approved by the DCP, CIRB and any other stakeholders, it cannot be implemented. All protocol deviations will be recorded on the Protocol Deviation Log (see Appendix F) and also in REDCap.

11.6 Sponsor or FDA Monitoring

The NCI, DCP (or their designee) or Wake Forest NCORP Research Base may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study. The use of the drug Ramipril in this protocol has been designated IND-exempt by the FDA and therefore does not require FDA monitoring.

11.7 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), FDA regulations and guidance, and NCI/DCP requirements, unless the standard at the site is more stringent. Wake Forest NCORP Research Base requires the records to be retained for at least 5 years after the study is discontinued and they should be notified prior to any planned destruction of material, unless the standard at the site is more stringent. NCI will be notified prior to the planned destruction of any materials.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Description

Study Design/Endpoints/Hypotheses
We propose a single arm pilot study to assess the feasibility of the use of Ramipril for GBM and the effect of Ramipril on neurocognitive function in patients using Ramipril in addition to stardard chemotherapy and RT for GBM. Patients will receive once daily oral Ramipril to be taken at the start of RT and continue for four months after completion of RT. Outcome assessments will be made at 1- and 4-month post-RT. The results of our trial will be compared to those from the control group of RTOG 0825. The objectives for this trial are: 1) to assess the retention rate of patients at 10 weeks of Ramipril treatment (6 weeks during RT and 4 weeks post RT) defined by compliance with drug therapy for at least 75% of doses during the 10 week period and completion of the composite neurocognitive battery, 2) to estimate the effect of 10 weeks of Ramipril on neurocognitive function in patients with GBM receiving chemoradiotherapy as measured by the Clinical Trial Battery Composite (CTB COMP) score, 3) to estimate the time to neurocognitive decline as assessed by the Clinical Trial Battery Composite (CTB COMP) score, 4) to estimate the effect of treatment on specific non-memory cognitive functions including attention, executive function, visuo-motor skills, working memory, a screening measure of global cognitive function, mood, quality of life, fatigue and sleep disturbance, 5) to collect preliminary

data on the presence of apolipoprotein epsilon (ApoE) isoform 4 serum (peripheral blood lymphocyte) test positivity as measured by quantitative PCR, and 6) To estimate neurocognitive function in surviving patients at the 4 month post RT endpoint. We will also explore differences in 4 month post RT outcomes by whether the patient received Optune® (also known as Tumor-Treating Fields or TTFields) as part of their standard treatment following RT.

Study hypotheses that will be explored include the following: 1) patient retention will be sufficiently high to proceed forward with a randomized trial of Ramipril; 2) patients receiving Ramipril will have better neurocognitive function (assessed using the Clinical Trial Battery Composite Score) compared to historical controls who did not receive Ramipril; 3) neurocognitive decline will be slower in patients receiving Ramipril; 4) patients receiving Ramipril will have better scores for the individual neurocognitive function tests; 5) patients receiving Ramipril will have better mood and quality of life and less fatigue and sleep disturbance.

12.2 Accrual and Feasibility

Sample Size
We will assess the dropout rate to inform us regarding the design of a subsequent randomized study. We will test the null hypothesis that retention < 65% versus the alternative hypothesis that retention ≥ 65%, with 90% power for detecting an alternative retention of 80%. The 65% threshold is related to retention rate, and is different from the 75% of doses required for compliance (Section 12.1). Assuming a 1-sided test at the 0.05 significance level, we obtain a sample size of 75 participants. The sample size calculation was conducted using NQery Advisor v7.0. Based on this calculation, we will plan for a sample size of 75, which will allow us to determine with a high level confidence whether or not the retention rate is sufficient to justify a subsequent study to this pilot.

We will also estimate the effect size in terms of reduction in neurocognitive decline in the intervention group as compared to historical controls. No formal statistical hypothesis will be tested for the purpose of declaring efficacy. The effect size, along with the estimate of the dropout rate, will be used to power and assess the feasibility of a planned subsequent randomized study. We expect an accrual rate of approximately 4 per month based on prior NCORP studies in similar brain tumor populations.

12.3 Primary Objective, Endpoint(s), Analysis Plan

The primary objective of this study is to assess the retention rate of patients at 10 weeks of Ramipril treatment (6 weeks during RT and 4 weeks post RT) defined by compliance with drug therapy for at least 75% of doses during the 10 week period and completion of the composite neurocognitive battery. The retention rate will be estimated by count and percentage with corresponding 95% exact binomial confidence interval. All patients receiving at least one treatment of Ramipril will be evaluable for retention.

Additionally, the Clinical Trial Battery Composite Score is derived from the arithmetic mean of the standardized scores from the HVLT-R total recall, HVLT-R Delayed Recall, HVLT-R Delayed Recognition Discriminability, Trail Making Test Part A, Trail Making Test Part B, and COWA. For CTB COMP, the effect size of neurocognitive change of patients receiving Ramipril versus patients who do not receive Ramipril in patients with newly diagnosed GBM using the control arm of RTOG 0825 as the comparison group will be calculated with a corresponding 95% confidence interval.

12.4 Secondary Objectives, Endpoints, Analysis Plans

All patients treated with at least one administration of Ramipril will considered as intent to treat in secondary analyses, although we do realize missing data may be a factor if many do not complete repeated neurocognitive assessments over the study duration. Per protocol analyses will also be performed for those successfully retained as defined in the primary objective.

Since patients will not be randomized in this study, all secondary analyses will consider adjusting for covariates that differ between the patients enrolled and the comparison cohort in RTOG 0825. Pre-specified covariates will include MGMT methylation, KPS, and extent of resection. While this study will not be used to declare efficacy, we will use repeated measures analysis of covariance (RMANCOVA) models to explore the effect of Ramipril across time and to determine if the baseline characteristics moderate the treatment effects. Pairwise interactions with treatment will be assessed. Residuals will be assessed to determine if the model assumptions (linearity, homogeneity of variances and normality) are met, and transformations will be used if necessary. Additionally, multiple imputation under various assumptions regarding the missingness will be used in conjunction with the mixed effects models to assess how sensitive our results are to our missingness assumptions.

Treating physician response rate will be summarized at each timepoint with corresponding 95% confidence intervals. Time to neurocognitive failure will largely follow the method reported in Gilbert *et al*. for evaluating if there is meaningful difference in the risk of cognitive progression[49]. Neurocognitive failure will be defined as the first decline on reliable change index on any of the individual cognitive tests[53]. In the presence of competing risks for neurocognitive failure, including GBM-related mortality risk, we plan to explore the use of competing risks methods for both descriptive statistics (e.g. the Kaplan-Meier curves) and competing risk regression analysis. Competing risk methods are needed because time to neurocognitive failure is not independent of mortality and ignoring events from competing risk will lead to biased results. The competing risk analysis will be based on the method proposed in Gray[53] and Fine and Gray[54] using SAS macro %CIF and PROC PHREG. Patient reported outcomes will be assessed as described above for the CTB COMP.

Exploratory subgroup analyses will be conducted for all 4 month post RT outcomes by whether the patient received Optune® (also known as Tumor-Treating Fields or TTFields) as part of their standard treatment following RT. Differences by Optune® for continuous outcomes will be assessed by two-sample t-tests where parametric assumptions hold; otherwise Mann-Whitney U tests will be applied. For categorical outcomes, Fisher's exact or Chi-square tests will be implemented. Corresponding 95% confidence intervals will also be presented for outcomes within each subgroup.

12.5 Retention and Compliance

Drop-outs are a difficult problem and one that is best handled proactively rather than retrospectively. We will make a concerted effort to minimize the number of drop-outs, beginning with the participants who are accrued. If a participant seems unwilling to participate or indicates that they may not be able to be compliant, we will not press them to participate. In addition, participants who refuse treatment at some point during the course of therapy will be encouraged to stay in the study and provide outcome data. Despite our best efforts, some data will be missing due to missed visits or participants refusing further participation. We propose to analyze the data using SAS Proc Mixed, a program that provides several computational methods for obtaining maximum likelihood estimates for repeated measures problems, allows for unbalanced designs, missing data at some times, structured or unstructured covariance matrices, and growth curve parameterizations of time effects. Additionally, we will employ multiple imputation methods to assess the treatment effect on the outcomes using the SAS multiple imputation procedures. Both the mixed models and imputation analyses assume participants are missing at random, that is, the missingness can depend on covariates and observed outcomes but not the missing outcomes.

This assumption that the missingness does not depend on the missing data cannot be tested completely since the data needed to test the assumption are missing. However, we will use logistic regression to see if we can determine which covariates, if any, are related to missingness, and these covariates will be used to create a propensity-to-be-missing score which will used to generate a stratified analysis as described by Baker et al[55]. Additionally, exploratory analyses using multiple imputations will assess the treatment effect over a range of assumptions regarding the missingness, allowing us to assess the sensitivity of our assumptions.

Compliance is defined as the number of pills consumed over the course of the trial divided by the ideal number that should have been consumed over that period. It will be calculated based on the patient's self-reported pill diaries. The primary analyses will be intent to treat, estimating treatment efficacy will include all randomized participants, regardless of compliance. Additional per protocol exploratory analyses will assess the treatment effect in those patients who were at least 75% compliant.

12.6 Reporting and Exclusions

Descriptive reports will consist of summary statistics (means, standard deviations, proportions, etc.) for participant characteristics and outcome measures by treatment arm, actual versus projected accrual, participation by the various NCORP sites, quality control information (retention, missing data, etc.), and a summary of toxicities and adverse events. Tables, graphs, and charts will be used to illustrate the data when appropriate. These reports will be prepared and presented to the WF DSMB committee every six months.

12.7 Evaluation of Toxicity

Evaluation of Toxicity and Adverse Effects of Ramipril
All patients will be evaluable for toxicity from the time of their first treatment with Ramipril. Toxicities will be quantified using the CTCAE v5.0 for Toxicity and Adverse Event Reporting. Fisher exact tests will be used to assess treatment differences in the incidence of individual toxicities, and logistic regression will be used to assess treatment differences in the incidence of any grade 3 or higher toxicity possibly, probably or likely related to Ramipril adjusting for baseline patient characteristics. In order to rule out cytoprotection of tumor by Ramipril, response rates will be compared to historical controls from RTOG 0825.

12.8 Evaluation of Response

Tumor response assessment will be based on treating investigator assessment and institutional standard of care and this assessment will be captured in this study.

13. REGISTRATION PROCESS

13.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site

staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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

13.2 Cancer Trials Support Unit (CTSU) Registration Procedures

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

Protocol documents are found on the CTSU website, but supplemental documents may be available on the Wake Forest NCORP Research Base website (https://wakencorp.phs.wakehealth.edu/dspLogin.cfm). Permission to view and download the neurocognitive test packet are restricted and is based on person specific training and is housed on the Wake Forest NCORP Research Base website.

IRB Approval

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

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

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

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

Additional Requirements

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

- An active Federal Wide Assurance (FWA) number;

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

Protocol Specific Requirements for WF-1801 Site Registration

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

- Neurocognitive training and certification through Wake Forest NCORP Research Base is required prior to participants being enrolled. At least one staff member per site must be certified.
- Site Open to Enrollment (SOTE) letter from WF NCORP RB, which is provided to the site once all site start-up activities have been completed.

Submitting Regulatory Documents:

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

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

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

Checking Site's Registration Status:

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

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

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

13.3 Patient Enrollment

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

Requirements for OPEN access:

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

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

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

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

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

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

13.4 Data Submission / Data Reporting

REDCap is a clinical data management system being used for data collection for this trial/study. Access to the trial in REDCap is granted through the Wake Forest NCORP Research Base. To access REDCap:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Must have a minimum of an AP registration type.
- Must be on the Wake Forest NCORP Research Base roster in NCORP-SYS for active study sites.

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

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons on the Study Site Role form in the Study Start-up Packet needing database access will be sent a study invitation e-mail from REDCap with their username and password. Please note, site users will not be able to access the study in REDCap until all required study specific trainings are completed.

Further instructional information will be provided after CTSU site approval is received and the site initiation packet is completed and returned to NCORP@wakehealth.edu. For any additional questions on REDCap contact the Wake Forest NCORP Research Base at 336-716-0891 or NCORP@wakehealth.edu.

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B
Data Submission Checklist

WF NCORP Research Base #1801 **Ramipril**	Site CTEP ID: _____ Staff Filling Out Form (initials): _____	PID: _____ Patient Initials: _____ Date (mm/dd/yyyy): _____

☐ Enrollment	Date Submitted
Eligibility/Enrollment in OPEN	
Patient Demographics/Health Behavior	
Signed Informed Consent	

☐ Baseline	Date Submitted
Baseline Data Collection Form	
NeuroCog & PROs booklet	
MRI report	
DNA (APOE genotype) Form	

☐ Week 1 - Titration	Date Submitted
Ramipril Titration Form – Week 1	
Ramipril Medication Diary, if end of month	
Submit any AE/SAEs per protocol	

☐ Week 2 - Titration	Date Submitted
Ramipril Titration Form – Week 2	
Ramipril Medication Diary, if end of month	
Submit any AE/SAEs per protocol	

☐ Week 3 - Titration	Date Submitted
Ramipril Titration Form – Week 3	
Ramipril Medication Diary , if end of month	
Submit any AE/SAEs per protocol	

☐ Week 4	Date Submitted
Ramipril Administration Form - Week 4	
Ramipril Medication Diary, if end of month	
Submit any AE/SAEs per protocol	

WF NCORP Research Base #1801 **Ramipril**	Site CTEP ID: _____ Staff Filling Out Form (initials): _____	PID: _____ Patient Initials: _____ Date (mm/dd/yyyy):_____

☐ Week 5	Date Submitted
Ramipril Administration Form – Week 5	
Ramipril Medication Diary, if end of month	
Submit any AE/SAEs per protocol	

☐ Week 6	Date Submitted
Ramipril Administration Form – Week 6	
NeuroCog & PROs booklet for week 6 - RT completion	
Ramipril Medication Diary, if end of month	
Submit any AE/SAEs per protocol	

☐ Week 10 (1 Month Post RT)	Date Submitted
Ramipril Admin. Assessment Form – Wk 10	
NeuroCog & PROs booklet for week 10	
MRI report	
Ramipril Medication Diary	
Submit any AE/SAEs per protocol	

☐ Week 14 (2 Month Post RT) – Telephone call	Date Submitted
Ramipril Admin. Assessment Form – Wk 14	
Ramipril Medication Diary	
Submit any AE/SAEs per protocol	

☐ Week 18 (3 Month Post RT) – Telephone call	Date Submitted
Ramipril Admin. Assessment Form – Wk 18	
Ramipril Medication Diary	
Submit any AE/SAEs per protocol	

☐ Week 22 (4 Month Post RT)	Date Submitted
Ramipril Admin. Assessment Form – Wk 22	
NeuroCog & PROs booklet for week 22	
MRI report	
Ramipril Medication Diary	
Submit any AE/SAEs per protocol	

WF NCORP Research Base #1801 **Ramipril**	Site CTEP ID: _____ Staff Filling Out Form (initials): _____	PID: _____ Patient Initials: _____ Date (mm/dd/yyyy):_____

☐ Week 26 (5 Month Post RT)	Date Submitted
Ramipril Phone F/U Form – Week 26	
Submit any AE/SAEs per protocol	
OFF-STUDY Form	

Other Forms:

- **Screening Logs** should be submitted at the end of each month. Sites should keep the original screening logs as source documents. (see Appendix C)
- **Adverse Event Form** should be used for adverse event reporting via REDCap and per protocol when needed.
- **Monthly Patient Ramipril Medication Diary** can be found in Appendix D of the protocol. Sites will transfer the information into REDCap for each diary. All diaries are considered source documents and should be kept by the site.
- **DNA (APOE genotype)** for blood collection submission and kits requests can be found in Appendix E of the protocol.

APPENDIX C
Ramipril Screening Log

WF NCORP Research Base #1801 **Ramipril**	Site CTEP ID: _____ Staff Filling Out Form (initials): _____	Page ____ of ____ Date (mm/dd/yyyy):_____

Instructions: For all patients screened for this study, complete this form indicating if patient was eligible or not. Please submit this information to NCORP@wakehealth.edu at least monthly by the last day of each month. This table can be copied, as needed, for additional screening log pages.

#	Patient Initials	Month/Year Screened	Eligible Y/N	Reason¥	Race¥	Ethnicity¥	Gender¥	Sex¥	Age

¥ Specific choices can be found on the following page.

Reason	**Race**	**Ethnicity**	**Gender**	**Sex**
1. **Investigator decision –** [be specific]	American Indian or Alaska Native	Hispanic or Latino	Female Gender	Male
2. **Ineligible** – [Why, be specific?]	Asian	Not Hispanic or Latino	Male Gender	Female
3. **Participant decision -** Transportation	Black or African American	Not reported	Unknown	Unknown
4. **Participant decision** – Time Involvement	Native Hawaiian or other Pacific Islander	Unknown		
5. **Participant decision** – Overwhelmed	White			
6. **Participant decision** – Did not like the study assessments/questionnaires	Not Reported			
7. **Participant decision** – Did not want to take Ramipril	Unknown			
8. **Participant decision** – Study too confusing				
9. **Participant decision** – Does not like research				
10. **Participant decision-**too sick or ill				
11. **Participant decision-** Desires compensation				
12. **Participant decision-** Other [be specific]				
13. **Other** [be specific]				

APPENDIX D

Monthly Patient Ramipril Medication Diary

Instructions: Use this calendar to record the number of pills that you take each day and as a reminder to take your medication. Be sure to bring this calendar and your pill bottle with you for **all** return appointments.

Please use only one calendar per month

Patient Initials ☐, ☐ ☐ (Last, First Middle)   Jan Feb Mar Apr May June July Aug Sept Oct Nov Dec   Year: 20____

Day of Week ____	Day of Week ____	Day of Week ____	Day of Week ____	Day of Week ____	Day of Week ____	Day of Week ____
☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____
☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____
☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____
☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____
☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____	☐ # of pills taken ____

Comments: ______________________________

____

____

Patient Signature ______________________________

Date ______________________________

For Office Use Only:

Research Base Patient ID: ______________

Site Name: ______________________________

WF NCORP Research Base WF-1801
Ramipril

Administration schedule for study medication (Ramipril)

_____ Week 1- take **one** 1.25 mg capsules of Ramipril by mouth per day.
Month/Date

_____ Week 2- take **two** 1.25 mg capsules of Ramipril (2.5 mg total) by mouth per day.
Month/Date

_____ Week 3- take **four** 1.25 mg capsules of Ramipril (5 mg total) by mouth per day.
Month/Date

_____ Week 4- take ____1.25 mg capsules of Ramipril by mouth per day and continue for
Month/Date 4 months after completion of radiation.

What should I do if I miss a dose of study medication (Ramipril)?
If you miss a dose of study medication and if it is less than 4 hours late, take that dose of study medication as directed. If greater than 4 hours, do not take this dose. Take your regular dose at the usual time the next day**.**

What medicines should I avoid while taking the study medication (Ramipril)?
Avoid potassium supplements (unless specifically prescribed by your physician), including salt substitutes that are high in potassium.
Caution should be used when taking NSAIDS, nonsteroidal anti-inflammatory agents, such as Aspirin, Motrin

Are there any expected adverse effects?
If you experience any of the following mild effects and feel they are related to your study medication (Ramipril), write them in the "comments" area. Discuss these with your research coordinator. Blurred vision, confusion, dizziness, faintness or lightheadedness when getting up suddenly from a lying or sitting position, sweating, unusual tiredness or weakness, cough, headache. There may be some risks that the study doctors do not yet know about.

When should I call my doctor?
The following may be signs of a more serious side effect and should notify your Doctor/research coordinator immediately: Arm, back, or jaw pain, chest pain or discomfort, chest tightness or heaviness, chills, cloudy urine, cold sweats, decrease in urine output or decrease in urine, concentrating ability, diarrhea, fainting, fast or irregular heartbeat, shortness of breath, seizures, unexplained bleeding or bruising, loss of liver function, lowered white blood cell count.

_____ at _____
Research Coordinator or Physician Phone number

If you have severe side effects, seek emergency care immediately.

APPENDIX E
Specimen Kit Request Form
WF-1801 Ramipril
DNA (APOE genotype)

Please use this form to request your initial and any additional specimen kits for WF-1801.

Contact Name: _____

Site CTEP ID: _____

Site Name: _____

Site Shipping Street Address: _____

(No P.O. Boxes) _____

Site Phone Number: _____

Site Fax Number: _____

Contact Person Email: _____

Initial Specimen Kit: Please complete and return this form to WF NCORP RB as part of your onboarding packet. An initial specimen kit will be shipped to the requesting site once this form has been received and processed.

Additional Specimen Kit: Once the initial kit has been assigned to a patient, sites should submit this Specimen Kit Request Form via email to Wake Forest NCORP Biospecimen Laboratory staff for an additional kit.

WF NCORP Biospecimen Lab
Attn: WF-1801 Specimen Kit Request
To: 7NCORP@wakehealth.edu
CC: NCORP@wakehealth.edu

If you have any questions or problems, please email NCORP@wakehealth.edu.

Collection of blood for APOE Genotype

1) Collect blood in a yellow-top Vacutainer tube (ACD is the anticoagulant). Fill this tube as much as possible (8 ml max), but at least halfway.

2) Invert the tube several times to mix the anticoagulant.

3) Do not allow the blood to remain at room temperature for more than 2 hours.

4) Store blood in the refrigerator at 4°C, may remain in the refrigerator for several days (e.g., over the weekend) before shipping. DO NOT FREEZE the blood.

Each tube will be labeled as follows:

Example: PID: _____

Date: _____ Time _____

Test Name	Tube Type	Special Instructions	Centrifuge	Specimen Temp
DNA	1 ACD Yellow Top 8 ml	None	Don't Centrifuge.	Ambient

Wake Forest Site Only: When labs have been collected, notify Wake Forest NCORP Biospecimen Lab personnel by phone at (336) 716-2581for lab pick-up.

Shipment of DNA blood samples for sites: (non-Wake Forest)

1) Samples should be shipped by FedEx priority overnight on Monday, Tuesday or Wednesday only.

2) Samples should be shipped in the containers provided with the frozen ice pack provided in the specimen kit.

3) Ship samples to:

K.KOURMAN & M. MORRIS
NCORP Biospecimen Lab
Phone: 336-716-2581
Bldg A1A Lab 230 c/o Delivery on Time
Wake Forest School of Medicine
RICHARD DEAN Bldg RECEIVING DOCK
391 TECHNOLOGY WAY
WINSTON-SALEM, NC 27101

4) Notify Wake Forest NCORP Biospecimen Lab when the samples are shipped 7NCORP@wakehealth.edu ; (336) 716-2581 and provide a tracking number.

5) **NOTE**: Site must comply with Shipping and Handling Instructions compliant with International Air Transport Association (IATA) Dangerous Goods Regulations. The shipping box is pre-labeled with the proper labels for compliance with IATA shipping regulations

Each specimen shipping kit will contain:

1) One pre-paid return shipping label, one re-sealable FedEx pouch for the shipping label; packing instructions and supplies for shipment of specimens to Wake Forest School of Medicine.

2) **Sites will provide:** Supplies needed for venipuncture, and packaging tape.

PID and Shipping Kit RL# must be entered below prior to shipping.

PID: _____

PID must be entered below prior to shipping.

INSTRUCTIONS: Send a copy of this form along with specimen samples to Wake Forest NCORP Biospecimen Laboratory. Place the original in the patient's protocol chart.

Blood Specimen Baseline

Date and time baseline blood sample drawn: (Please use military time)

Date Time

M	D	Y	H	M

FOR LAB USE ONLY

Time Point	Date Received	Tubes Intact (Y/N)	Usable (Y/N)	Date Analyzed
Baseline Blood				

APPENDIX F

Protocol Deviation Log

Purpose: To record all protocol deviations that occur at a study site

Audience/User: Study coordinators, principal investigators (PIs), other site staff

Details: This tracking log should provide a comprehensive list of all protocol deviations that occur at a study site. It is required for both observational and interventional clinical research studies.

This tool is complementary to, and does not replace, the form reporting individual protocol deviations to the Central Institutional Review Board for the National Cancer Institute (CIRB). Deviations should be reported to the CIRB and others, as required.

Best Practice Recommendations:

- Record protocol deviations in the tracking log as they occur, to ensure completeness and accuracy of the data.
- The site PI should sign each form after it has been completed.
- Number each page and maintain this log in the Regulatory Binder.
- Store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
- At the conclusion of the study, identify the final page of the log by checking the box in the header.

Notification of WF NCORP RB:

- Sites should notify WF NCORP RB by documenting any protocol deviations within REDCap within 5 days (120 hours) of discovery.

WF NCORP Research Base #1801 Ramipril	Site CTEP ID: _____ Staff Filling Out Form (initials): _____	Page _____ of _____ ☐ Final page Date (mm/dd/yyyy):_____

Protocol Deviation Log

Ref No.	PID	Date of Deviation	Date Identified	Deviation Description	Type§	Resulted in AE?	Did Subject Continue in Study?	Meets cIRB Reporting Req. (Yes/No)	cIRB Reporting Date
1									
2									
3									
4									
5									
6									
7									

§**Deviation Types**

A – Consent Procedures
B – Inclusion/Exclusion Criteria
C – Concomitant Medication/Therapy
D – Laboratory Assessments/Procedures
E – Serious Adverse Event Reporting
F – Randomization Procedures/Study Drug Dosing
G – Visit Schedule/Interval
H – Other

Investigator Signature: _____ Date:_____