

Comprehensive Cancer Center of Wake Forest University
CCOP Research Base Protocol #91105

Title: Phase III Double Blind, Placebo Controlled Study of Donepezil in Irradiated Brain Tumor Patients

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

Institutions not aligned with WFU CCOP Research Base will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <https://members.ctsu.org>
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the CCCWFU CCOP Research Base Data Management Center (DMC). **Case report forms** (with the exception of patient enrollment forms), **signed consents, clinical reports, symptom/ medication diaries, and transmittals** must be sent via mail or fax to the CCCWFU CCOP Research Base DMC unless otherwise directed by the protocol. Your institutions standard fax transmittal cover sheet should accompany all data submissions. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by CCCWFU CCOP Research Base DMC. Please send query responses and delinquent data to CCCWFU CCOP Research Base DMC and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the CCCWFU CCOP Research Base DMC.

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<p>To submit site registration documents:</p>	<p>For patient enrollments:</p>	<p>Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:</p>
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206</p>	<p>CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays)</p> <p>[Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm.]</p>	<p>CCCWFU CCOP Research Base Attn: Data Management Center Outpatient Comprehensive Cancer Center Medical Center Boulevard Winston Salem, NC 27157-1030 FAX: 336-713-6476</p> <p>Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</p>
<p>For patient eligibility or treatment-related questions <i>contact the Research Nurse listed on the protocol cover page..</i></p>		
<p>For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at https://members.ctsu.org</p>		

CTSU logistical information is located in Appendix 17.

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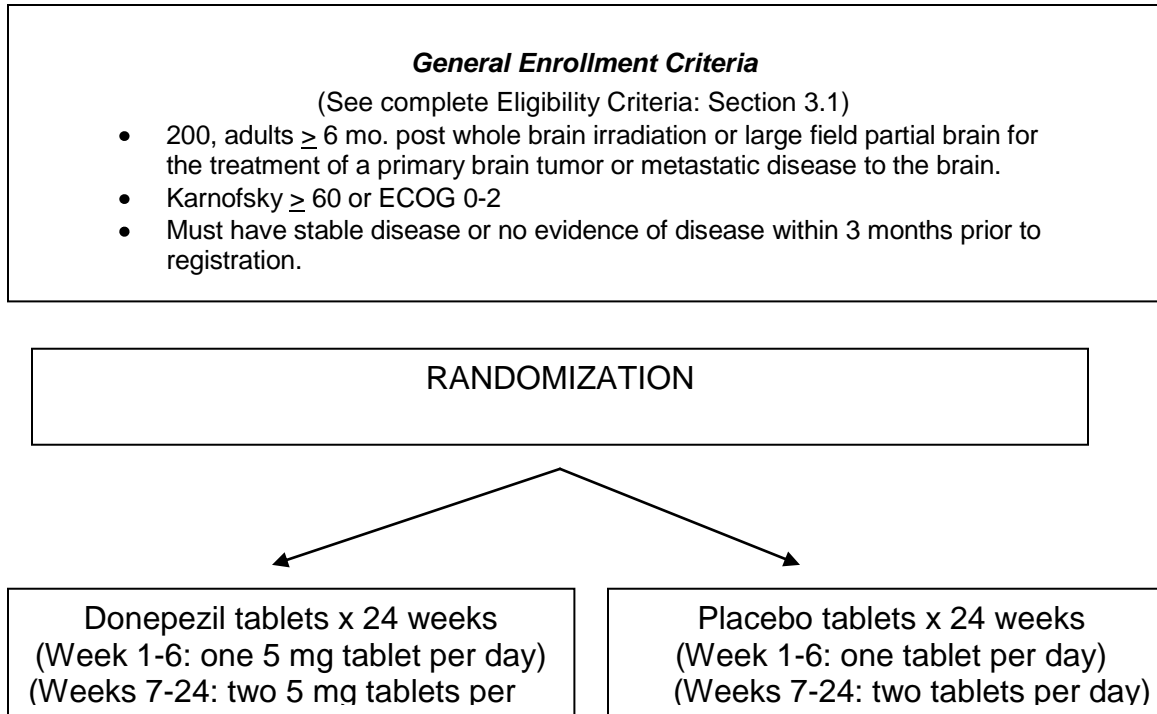
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Title: A Phase III Double Blind, Placebo Controlled Study of Donepezil in Irradiated Brain Tumor Patients

SCHEMA



Stratification will be performed by irradiation type and accrual site.

Study Procedures	
Baseline:	Enrollment; randomization; baseline assessment (neurocognitive battery, fatigue, mood and quality of life questionnaires)
Weeks 1-6:	Administration of donepezil (5 mg daily) or placebo
Week 6:	Phone interview for assessment of toxicities; if indicated increase donepezil or placebo to 10 mg/day starting week 7
Week 12:	Return to clinic for re-assessment of toxicities and study outcomes (neurocognitive battery, fatigue, mood, and quality of life questionnaires)
Week 24:	Return to clinic for re-assessment of study outcomes (neurocognitive battery, fatigue, mood, and quality of life questionnaires); termination of study
Sample Size: 200	

1. BACKGROUND

1.1 STUDY DISEASE:

Cognitive impairment associated with primary or metastatic brain tumors and their treatments, including radiation therapy, occurs in a substantial proportion of patients with 10% of patients developing progressive dementia, and 50% to 90% showing deficits when assessed with sensitive tests of cognitive function (1-3). Clinically, patients frequently complain of a neurocognitive symptom cluster that include fatigue, subjective confusion, and cognitive impairment (e.g., decreased attention and concentration, poor short term memory, and expressive language difficulties). The neurocognitive symptom cluster occurs with distressed mood (e.g., depression) and reduced quality of life.

Late radiation-induced brain injury is defined as that which occurs 6 months or more following a course of partial or WBI(4-7). The traditional view of the pathophysiological mechanism of late radiation-induced brain injury is that the vasculature (endothelial cells) (8) and parenchyma (oligodendrocytes) (9) are the prime targets of ionizing radiation. Thus, the predominant histological changes seen in radiation-induced brain injury were vascular abnormalities (decrease in vessel number and length as well as endothelial hyperplasia), demyelination, and white matter necrosis (10-12). Hopewell and Wright (8) summarized their view of radiation-induced brain injury as follows:

- The primary target of radiation injury to the brain is the vasculature
- Endothelial cell loss and reduced vascular density leads to ischemia and demyelination, followed by white matter necrosis
- Cytokines are expressed (e.g. TNF- α , IL-1 β) leading to inflammation

Based on this traditional view, manifestations of late radiation-induced brain injury, resulting presumably from ischemia and demyelination, range from frank radiation-induced white matter necrosis to cognitive sequelae manifest as impaired learning and memory. Cytokine expression more likely results in symptoms contributing to a decline in quality of life (QOL) such as fatigue and mood disturbances, primarily depression and anxiety. The incidence of radiation-induced brain injury is unknown and likely underreported for several reasons, including lack of routine assessment, utilization of non-specific tests of cognitive function, similarity between symptoms of brain tumor recurrence and radiation injury, as well as poor long-term survival of patients with primary or metastatic brain tumors. The reported incidence of radiation necrosis or dementia varies in the literature. With partial-brain irradiation, the incidence of frank radiation necrosis is 1% at doses of 5000 cGy and 5% at doses of 6500 cGy (13). DeAngelis et al (14) found that the incidence of progressive and fatal radiation-induced dementia was 11% in patients receiving WBI with ≥ 3 Gy per fraction for brain metastases. Crossen et al reviewed nearly 750 patients in 29 studies in the contemporary medical literature and found that 12% had "clinically apparent" dementia following WBI (4). Thus the incidence of cognitive impairment including frank dementia, fatigue, mood disturbance and reduced QOL is high among patients following P/WBI.

RADIATION-INDUCED COGNITIVE IMPAIRMENT

Precise estimates of the incidence of specifically radiation-induced brain injury are unknown and likely underreported for several reasons, including lack of routine assessment, utilization of non-specific tests of cognitive function, similarity between symptoms of brain tumor recurrence and radiation injury, as well as poor long-term survival of patients with primary or metastatic brain tumors. Existing estimates of the incidence of radiation-induced dementia vary from 1% at doses of 5000 cGy following PBI to 5% at doses of 6500 cGy (27). DeAngelis et al (48) found

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that the incidence of progressive and fatal radiation-induced dementia was 11% in patients receiving WBI with ≥ 3 Gy per fraction for brain metastases. Crossen et al. reviewed 29 studies including nearly 750 patients and found 12% had "clinically apparent" dementia following WBI (39).

When considering less severe cognitive dysfunction than dementia incidence estimates increase substantially. Brown et al (49) observed an 8%, 5%, and 5% incidence of cognitive decline at 1-, 2-, and 5-years, respectively, following PBI in 203 adults with supratentorial low-grade glioma. In another study 50% to 67% of patients receiving low-dose (20-40Gy) prophylactic cranial irradiation for small cell lung cancer who underwent routine post-radiation cognitive testing had moderate to severe cognitive deficits (7;8). This is similar to the 40-60% incidence of worsened cognitive functioning (executive function, fine motor control, and memory) following accelerated radiation therapy followed by PCV chemotherapy for anaplastic gliomas (50;51). Ten percent of these patients had severe dementia requiring full-time care. Thus the incidence of measurable cognitive impairment including dementia among patients receiving cranial irradiation is quite high.

The specific cognitive impairments associated with brain tumors and their treatments including cranial irradiation are many including deficits of information-processing speed, frontal lobe executive functions, memory, sustained attention, verbal fluency, and bilateral motor coordination (50;52-54). Hochberg and Slotnick identified deficits in problem-solving, memory, sustained attention, complex perceptual tracking, and manual dexterity in a small group of long-term survivors with cerebral astrocytoma (54). In a larger series of malignant glioma patients, Imperato et al found that memory impairment and gait disturbance were the two most common neurologic sequelae of postoperative radiation therapy (55). In a small study by Archibald et al, malignant glioma patients were treated with postoperative radiation therapy with or without chemotherapy. Verbal memory and sustained attention were the most impaired cognitive functions at baseline, and verbal learning and flexibility in thinking showed the greatest tendency to decline over time (52). In a recent prospective study of WBI with or without the investigational radiosensitizer motexafin gadolinium in patients with brain metastases, Meyers et al reported a 91% incidence of baseline cognitive impairment. Sensitive tests of cognitive function were administered monthly to assess memory, verbal fluency, executive function, motor speed and dexterity. Improvement was observed in executive function and memory; and baseline test scores correlated with tumor volume and predicted survival (9)

In a recent study of ≥ 6 month survivors of large field or WBI conducted at Wake Forest University School of Medicine by the present research group (see Preliminary Studies for description), 34 patients were enrolled in a Phase 2 (open-label) study of donepezil on cognitive impairment, mood and quality of life (82). Items from the Functional Assessment of Cancer Therapy with Brain instrument (56), a well-validated cancer QOL questionnaire for patients with brain cancer, indicated an extremely high level of cognitive symptoms at baseline. Specifically most patients reported difficulty concentrating (97%), remembering new things (94%), finding the right words (97%), expressing thoughts (83%), putting thoughts together (94%), and putting thoughts into action (91%). These patients also indicated moderate to severe subjective confusion.

Thus, a large proportion of patients receiving P/WBI suffer cognitive impairments that can be objectively measured and subjectively experienced and that erode mood and quality of life. If this neurocognitive symptom cluster can be improved with tolerable treatments, then patients' mood and quality of life are likely to improve as well. Fortunately there are several choices of medications used successfully in patients with cognitive impairments caused by diseases such as Alzheimer's disease where the primary symptoms are neurocognitive. Donepezil, a well

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tolerated acetylcholinesterase inhibitor with demonstrated efficacy with dementia patients, is presently the most widely prescribed 'cognitive enhancer'.

1.2 STUDY AGENT

Donepezil hydrochloride (Aricept) is a reversible inhibitor of the enzyme acetylcholinesterase. It is currently FDA approved for use in the treatment of mild to moderate dementia of the Alzheimer's type. Donepezil hydrochloride is available for oral administration in 5 or 10 mg film-coated tablets. Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. The concentration of acetylcholine is increased by reversible inhibition of its hydrolysis by acetylcholinesterase.

1.3 RATIONALE

1.3.1 TREATMENT OF DEMENTIA SYMPTOMS WITH ACETYLCHOLINESTERASE INHIBITORS

Alzheimer's disease, the most common cause of dementia, is clinically characterized by a gradual decline in cognitive functioning and associated behavioral impairment. AD produces a deficit in central cholinergic transmission caused by degeneration of the basal forebrain nuclei (57-59). Choline acetyltransferase and acetylcholine levels are significantly reduced in patients with Alzheimer's dementia (58;60-62). In recent years progress has been made in the pharmacological treatment of dementia. Improvement in cholinergic neurotransmission has been achieved by reducing acetylcholine synaptic degradation with cholinesterase inhibitors. Acetylcholinesterase inhibitors have demonstrated beneficial effects on cognitive, behavioral, and functional symptoms of AD (63-67) and have become first-line treatment in patients with mild-to-moderate AD (68). Donepezil is a piperidine derivative, which non-competitively and reversibly inhibits AChE; it is highly selective for AChE, and binds to plasma proteins; and it is well-tolerated (17). A recent meta-analysis of randomized, double-blind, placebo-controlled group trials using donepezil have supported its efficacy in patients with mild-to-moderate AD. Wilkinson et al. reported significant cognitive improvement after only 12 weeks of treatment with donepezil (69). McKeith et al. found significant improvement in cognitive and behavioral symptoms in AD patients with moderate-to-severe dementia (70). Donepezil improves cognitive functioning in healthy young adults (71), and in patients with Parkinson's disease (72), multiple sclerosis (73) and traumatic brain injury (74). In addition to the known direct effects on neuronal function, donepezil also increases cerebral perfusion in critical brain areas related to cognitive processing (75). As noted above (Section B2) there is also evidence that cranial irradiation adversely affects cholinergic pathways in the brain and in particular the hippocampus, important in learning and memory and mood regulation. Given its efficacy and tolerability with dementia patients, donepezil may be a suitable pharmacological agent for reducing radiation-induced cognitive impairment.

1.3.2. TREATMENT OF RADIATION-INDUCED COGNITIVE IMPAIRMENT

The first interventional agent used to reduce the cognitive morbidity and improve the QOL in irradiated brain tumor patients was the amphetamine methylphenidate. The choice of this drug was somewhat empiric, based on the assumption that a central nervous system stimulant might affect both QOL and cognition. Weitzner and Meyers reported significant improvements in both cognitive function (visual-motor speed, verbal memory, expressive speech, executive function, and fine-motor coordination) and QOL following administration of methylphenidate (76;77). To our knowledge, there have been no specific tests of other agents until recently.

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In 2000, a diverse group of clinical and basic science investigators from the Wake Forest University School of Medicine (WFUSM) joined together to develop mechanistically-appropriate interventions for patients with radiation-induced brain injury suffering from poor QOL and cognitive dysfunction, based on a more contemporary view of radiation-induced brain injury (18). Recent findings suggest that the classic model of parenchymal or vascular target cells is overly simplistic. Pathophysiological data from a variety of late responding tissues, including the CNS, indicate that the expression of radiation-induced normal tissue injury involves complex and dynamic interactions between several cell types within a particular organ (19-22). In the brain, these include not only the oligodendrocytes and endothelial cells, but also the astrocytes, microglia and neurons. These now are viewed not as *passive* bystanders, merely dying as they attempt to divide, but rather as *active* participants in an orchestrated, yet limited, response to injury (12;23). This new paradigm offers an exciting new approach to radiation-induced normal tissue morbidity, i.e., the possibility that radiation-injury can be modulated by the application of therapies directed at altering steps in the cascade of events leading to the clinical expression of normal tissue injury. Since such a cascade of events does not occur in tumors, where direct clonogenic cell kill predominates, such treatments should not negatively impact antitumor efficacy. Building on this conceptualization, our investigative team conducted several related studies of different agents including a Phase II study of donepezil in patients following partial and whole brain irradiation that provided very encouraging pilot data for this protocol.

As a result, we hypothesize that radiation induced neuronal injury (as well as injury produced by the tumor and other treatments preceding cranial irradiation) decreases levels of the neurotransmitter acetylcholine in the brain, and predict that an acetylcholinesterase inhibitor will improve the neurocognitive symptom cluster in patients following P/WBI and that a reduction in neurocognitive symptoms will improve patient mood and overall quality of life.

2. OBJECTIVES

2.1 Primary Protocol Objectives

To determine whether administration of donepezil for 24 weeks to ≥ 6 month survivors of partial or whole brain irradiation will improve the neurocognitive symptom cluster (objective cognitive performance deficits + subjective cognitive functional impairments) as compared to placebo. The specific hypothesis to be tested is:

Objective 1A. Overall cognitive performance will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

Objective 1B. Subjective cognitive complaints/symptoms will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

Objective 1C. Fatigue will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

2.2 Secondary Protocol Objectives

To determine whether administration of donepezil for 24 weeks to ≥ 6 month survivors of partial or whole brain irradiation will improve mood and QOL as compared to placebo. The specific hypothesis to be tested is:

Objective 2A. Cancer-related quality of life will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

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Objective 2B. Overall mood will be improved in donepezil treated patients as compared to placebo treated patients at 24 weeks.

3. PATIENT SELECTION

3.1 Eligibility Criteria

- Adults ≥ 18 years old.
- Life expectancy of at least ≥ 30 weeks.
- Must have received a prior course of at least 30 Gy fractionated whole or partial brain irradiation for treatment of a primary brain tumor or metastatic disease to the brain.
- Must have completed radiation ≥ 6 months prior to enrollment and have no radiographic evidence of brain disease, or stable brain disease defined as no evidence of tumor progression in the 3 months prior to enrollment.
- Patients who have undergone one or more treatments with single fraction stereotactic radiosurgery (SRS) in addition to whole or partial brain irradiation are eligible.
- Radiation treatment records must be available for all prior radiation treatments (external beam and/or SRS).
- Patients who have received PCI (prophylactic cranial irradiation) are eligible.
- Karnofsky Performance Status must be ≥ 60 or ECOG 0-2.
- Treatment with steroids, anti-cholinergics, anti-epileptics, anti-depressants, and /or sedatives/benzodiazepines is acceptable, but the patient must be on a stable or decreasing dose at the time of study entry.
- Patients using narcotic analgesics on a stable dose and/or prn basis are eligible.
- Patients currently on a stable dose of Methylphenidate or Dexamphetamine are eligible.
- For patients with brain metastases, if extracranial primary or metastatic disease is present, it must have responded to local and/or systemic treatment. Must be stable in the 3 months prior to enrollment.
- Must not be receiving chemotherapy at the time of enrollment.
- Patient must not have any planned therapy, including surgery, brain radiation of any type, chemotherapy, or immunotherapy during the next 30 weeks for brain or extracranial primary metastatic disease.
- Hormonal therapy for patients with breast or prostate cancer is acceptable.
- Breast patients receiving therapy with Herceptin are allowed.
- Patients must be able to give informed consent to participate in the study, including signing the consent form.
- Patients must have a telephone.

3.2 Exclusion Criteria

- Patients cannot be currently taking dementia drugs, cognitive enhancers, neuroleptics, and/or anti-parkinsonian agents. For patients who have used these drugs in the past, they must not have used them in the 2 weeks prior to enrolling on the study.
- Hypersensitivity to donepezil.
- Patients may not currently be taking Ketoconazole or Quindine
- Arrhythmias including bradycardia or heartblock
- Patients who have received, GliSite or other type of brain brachytherapy, (Gliadel Wafers permitted) convection enhanced delivery of immunotoxins, and/or any other investigational modalities for treatment of their brain tumor. The effects of donepezil on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study

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participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

- It is unknown whether donepezil is excreted in breast milk, for this reason women who are currently breast-feeding are not eligible for this study.

4. DRUG THERAPY

4.1 Drug Information

4.1.1 Availability

Donepezil hydrochloride (Aricept) is a reversible inhibitor of the enzyme acetylcholinesterase. It is currently FDA approved for use in the treatment of mild to moderate dementia of the Alzheimer's type. Donepezil hydrochloride is available for oral administration in 5 or 10 mg film-coated tablets. It is to be stored at room temperature (15°C to 30°C). Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. The concentration of acetylcholine is increased by reversible inhibition of its hydrolysis by acetylcholinesterase. Donepezil has a relative oral bioavailability of 100%. It reaches peak plasma concentrations in 3 to 4 hours. The elimination half-life is about 70 hours and steady state is reached within 15 days. Donepezil is metabolized by CYP 450 isozymes 2D6 and 3A4 and undergoes glucuronidation. In a small study of patients with cirrhosis, the clearance of donepezil was decreased by 20% compared to healthy controls. In a few patients with severe renal impairment, the clearance was unchanged compared to healthy controls. There have been no interactions of donepezil with furosemide, digoxin, warfarin, theophylline, or cimetidine. Inducers of CYP 2D6 and CYP 3A4 could increase the rate of elimination of donepezil but this has not been demonstrated clinically. These drugs include phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital. Ketoconazole and quinidine inhibit donepezil metabolism in vitro but it is not known whether there is a clinical effect. The most frequent adverse clinical events are due to donepezil's cholinomimetic effect. These include anorexia, nausea, vomiting, diarrhea, fatigue, insomnia, and muscle cramps. These are often mild and transient, resolving with continuation of the drug. There are a few more side effects noted when the drug is titrated from 5mg to 10mg in one week vs. six weeks. Nausea occurred in 19% after one week titration compared to 6% after 6 weeks. Other side effects which occurred in >10% of patients were diarrhea (15% vs. 9%) and insomnia (14% vs. 6%) both being more common after a one week titration. In the proposed study, a 6-week titration from 5 mg to 10 mg (two 5 mg tablets) will be used. If a study patient does not tolerate 10 mg/day, they will revert to the 5 mg/day dose for the remainder of the study.

4.1.2 Agent Ordering and Distribution

Donepezil (Aricept) is manufactured and marketed by Eisai Inc., Teaneck NJ and distributed by Roerig Division of Pfizer Inc, New York, NY. Pfizer, Inc. will provide donepezil and placebo at no cost for patients participating in this study.

The components of conducting this Phase III Randomized placebo controlled double blind study of this magnitude include drug procurement (of donepezil and placebo), drug storage and inventory management, administration to ensure proper randomization and maintain fidelity of the double blinding, processing and preparation of study drug (donepezil and placebo) into properly labeled bottles, and distribution of drug to participating sites. This will be handled by Biologics, Inc., Durham, NC.

At randomization, Biologics, Inc will automatically receive notification the patient has been enrolled. Biologics will call the site to obtain further information. Stratification will be performed by irradiation type and accrual site.

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Study medication should be stored at room temperature. (15°C to 30°C /59°F to 86°F)

4.1.4 Preparation – N/A**4.1.5 Toxicities**

Common adverse effects include anorexia, diarrhea, nausea, vomiting, fatigue, insomnia, muscle cramps. If side effects become intolerant for the patient, he/she may be withdrawn from the study at the discretion of the physician.

4.1.6 Administration

Drug will be self-administered orally on an outpatient basis.

4.2 Treatment Plan

The research PI or designee at each participating Research Base site, which may include the clinic physician, resident, research nurse or research assistant, may review cancer registry and medical chart information to identify patients eligible for this protocol. Patients identified as eligible by using these methods will be asked to join the study during their next clinic visit or consult. Patients not scheduled for a clinic visit within the next 6 weeks will be sent a letter from their physician informing them about the study, and indicating that a research nurse/assistant will be calling them within the next 10 days to tell them more about the study and to see if they are eligible to participate.

Patients meeting initial eligibility criteria and who agree to participate in the study will sign informed consent, complete the neurocognitive battery and study instruments. Patients will be instructed in the self-administration of study drug. For six weeks, patients will take one tablet each evening. Pending satisfactory toxicity review in Week 7 the dose will be increased to two tablets daily (10 mg) with a similar change in the placebo group.

For the first 6 weeks of the study patients will take a single 5 mg Donepezil or placebo oral dose in tablet form. Following a positive toxicity review in Week 7, patients will take two 5 mg Donepezil tablets daily (10 mg total) or placebo through Week 24 at study termination. It will be recommended that patients take tablets (donepezil and placebo) in the evening with or without food. Reported adverse events and potential risks are described in Section 4.1.5. Study outcomes will be assessed at baseline (Week 0), Week 12 and Week 24.

Patients will receive gift certificates totaling \$40. Patients will be given one \$20 gift certificate at the baseline visit and one \$20 gift certificate when they complete the study. Sites should contact Robin Rosdhal at (336) 713-6519 or rosdhal@wfubmc.edu to request gift certificates to distribute to patients. At the completion of the study, all unused gift certificates should be returned to Robin Rosdhal.

4.2.1 Neurocognitive Battery

The neurocognitive battery will consist of 3 test booklets: Baseline Booklet, 12 Week Booklet and 24 Week Booklet. Each booklet will be completed by the patient at the Baseline, 12 week, or 24 week clinic visit. A description for each test is listed below:

Cognitive Performance (Objective)

1. Controlled Oral Word Association Test (COWA). The COWA (88) measures speed of mental processing, verbal fluency, and executive function. Subjects are asked to name as many words as possible all beginning with a specified letter. A total of three trials are administered, each with a different letter (C-F-L). The score on the COWA is the total

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number of words named across the three trials minus repetitions. The COWA has two equivalent forms (C-F-L and P-R-W) that will reduce practice effects. Internal consistency reliability ($\alpha=0.83$) and test-retest reliability ($r = 0.74$) are excellent (2).

2. Hopkins Verbal Learning Test-Revised (HVLT). The HVLT-R (101) measures verbal learning and memory. It consists of a 12-item word list which is read to subjects on three successive learning trials. The HVLT has two equivalent forms to reduce practice effects. One set is for Baseline and 24 week assessments, and the other set is for the 12 week assessment. **You must use the forms indicated for Baseline, 12 week, and 24 weeks assessments.** Free recall scores are recorded for each learning trial. After a 20-minute interval during which subjects complete other non-interfering tasks and questionnaires they are asked to recall the target words. Lastly, a yes/no recognition task is then presented in which subjects are asked to identify all target words by responding "yes," and to reject 12 non-target words by responding "no". The HVLT has six equivalent alternate forms (99-100). Test-retest reliability of the HVLT-R is quite good (0.74). The test is brief, taking only 10 minutes to administer, and it is well-tolerated by compromised (geriatric and dementia) populations. Six equivalent forms minimize confounding by practice effects. Scores for immediate recall (total of three trials), delayed recall (total number of words recalled after 20 minutes), and recognition (total number of words correctly identified) will be the variables derived from the HVLT.
3. Trail Making Test, Parts A & B (TMT-A, TMT-B). Part A of the TMT (85) measures attention and visual motor speed and requires subjects to connect 25 numbered circles in the proper sequence (1-2-3-...) as quickly as possible. TMT-B is similar except subjects are required to connect dots in an alternating numerical and alphabetical sequence (1-A-2-B-...). TMT-B with its added complexity and set shifting requirements is a widely used measure of executive function. The score for TMT-A and TMT-B is the total time in seconds required to complete the task. Scores can also be generated for number of errors and number of circles correctly connected. The TMT has excellent reliability and validity(85).
4. Modified Rey-Osterreith Complex Figure (mROCF). mROCF(87) is a test of visuomotor skills and non-verbal memory. Subjects must copy a complex figure in a specified time period. They are then asked to draw the figure from memory. Several minutes later during which subjects are completing other non-interfering tests and questionnaires they will be asked to redraw the figure from memory. The score for each drawing is the sum of figure elements recalled using standardized scoring criteria.
5. Digit Span Test (DST). The DST (86) assesses attention and working memory. It requires respondents to repeat back gradually increasing spans of numbers. Seven series of two spans of each length are presented and repeated forwards and seven other series are repeated backwards. A total score is the sum of the longest span forwards and backwards.
6. Grooved Pegboard (GP). The GP(89) task measures motor performance. The respondent inserts 25 small pegs with a key tip into 25 randomly positioned slots, first with the dominant hand and then with the non-dominant hand. The score is the total number of pegs correctly inserted in the time allotted. We will combine the two scores for a single score. **Pegboards will be provided on loan by the WFU Research Base. A pegboard will be shipped to the site upon request. Send requests to June Fletcher-Steede at jsteede@wfubmc.edu. Pegboards must be returned to WFU Research Base at completion of the study.**

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To assess the effect of donepezil on cognitive functioning we will calculate an overall cognitive composite score, the mean of all 6 cognitive tests standardized (z-score). Secondary analysis will examine effects on specific cognitive functions.

4.2.2 Subjective Complaints/Symptoms, Mood, Fatigue and Cancer-Related Quality of Life

The Functional Assessment of Cancer Therapy-Brain (FACT-Br) scale was developed to provide information about health-related QOL that is specific to cancer patients (23). The FACT-Br consists of 27 questions with five domains assessing physical well being (7 items), social/family well-being (7 items), emotional well-being (6 items), and daily functional well-being (7 items). A 19-item Brain subscale includes items specific to cancer patients with brain tumors (58) and will be our measure of subjective complaints/symptoms (Specific Aim 1). A FACT-Br Total score will be used in the primary analysis (Specific Aim 2); individual subscale scores will be used in secondary analyses to assess domain-specific effects of donepezil. The FACIT-Fatigue scale will be the outcome measure for Specific Aim 1. The Profile of Mood States will be used to measure overall distressed mood (Specific Aim 2). The POMS yields subscale scores for major mood states: anxious, angry, depressed, confused, and fatigued. The Physical Health Questionnaire is a brief screen for major depression and will also be administered.

Assessing Participant Emotional Distress

Included in the test booklet is the Patient Health Questionnaire (PHQ), the last questionnaire in each booklet). The PHQ assesses depressive symptom severity which can co-occur with serious medical conditions like brain tumors. The value of the PHQ is to ascertain who among study participants is experiencing moderate to severe distress so s/he can be encouraged to seek treatment. The study drug is not known to cause or increase depression.

The PHQ is scored by first assigning a numeric value to each of the 9 items ('Not at all'=0; 'Several days'=1; 'More than half the days'=2; 'Nearly every day'=3) and then totaling item scores. The minimum score is 0 and the maximum score is 27; a score ≥ 19 indicates moderate to severe depressive symptom severity.

At the end of each assessment period, add up the total score of the PHQ. If it is ≥ 19 or if item '9' is scored 1, 2, or 3, then take a few minutes to discuss the participant's distress and what s/he is doing to manage it. You should mention:

- Distress is common among persons with serious medical conditions
- Treatments are available that might reduce the distress
- Discussing your distress with your doctor, family, friends, pastor or specialist (counselor, therapist) can be helpful
- Offer assistance making a referral to a mental health specialist if the person is interested.
- Inform the participant that you will notify the physician overseeing this study at the site as well as the study PI (Drs. Rapp and Shaw at Wake Forest University School of Medicine) (Steve Rapp: srapp@wfubmc.edu (336) 716-6995, Ed Shaw: eshaw@wfubmc.edu (336) 713-6535)
- Specifically ask:
 - In the past week, have you thought you would be better off dead or wished you were dead?
 - In the past week, have you wanted to harm yourself?
 - In the past week, have you thought about suicide?
 - In the past week, have you developed a suicidal plan?
 - In the past week, have you tried to kill or hurt yourself?

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- Do you think you might commit suicide?
- If participant indicates s/he is **currently actively suicidal (i.e., has a plan and intent), ask him/her to remain with you while you contact the site physician. If that is not possible, ask for permission to contact a family member.**
 - Inform the site physician or family member and seek their guidance on how to get immediate help for the individual.
 - If no one is available you can call 911 or accompany the individual to the nearest Emergency Department. This is exceedingly rare in studies such as this.
- If participant is **not actively suicidal, encourage him/her to speak with his/her doctor, family, friends, pastor or mental health professional about getting additional help.**
- Note occurrence on PHQ Summary Sheet.

4.3 Dose Modification

4.3.1 Toxicity Management

All adverse events (i.e., treatment toxicities), whether observed by the investigator or reported by the patient, must be recorded using CTC Version 3.0, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness. Study patients will take a single oral tablet (5mg of donepezil or placebo) everyday for 6 weeks. Research personnel will contact patient via telephone during the 6th week of study drug. Patients will be evaluated using a toxicity assessment form. If patient is tolerating donepezil/placebo without any unacceptable toxicities, donepezil/Placebo dose will be increased to two tablets donepezil or placebo tablets starting on Week 7 and continuing through Week 24. Patients will have office visits including toxicity assessment at week 12 and week 24.

It is recommended that patients take tablets (donepezil/Placebo) in the evening with or without food. If donepezil 10mg/placebo is not tolerated, the treating physician should decrease dose to donepezil 5mg/placebo (one tablet) for the remaining study period. Any unacceptable drug-related (Grade 3 or greater) toxicities while patient is taking one pill per day will require patient to have donepezil/placebo discontinued. However, if the patient is experiencing insomnia on the 5mg or 10mg dose, the donepezil dose can be taken in the morning at the physician's discretion.

4.3.2 Toxicity Criteria – refer to section 14.1

Toxicity will be determined using the revised NCI Common Toxicity Criteria (CTC) version 3.0 for Toxicity and Adverse Event Reporting. Any drug related toxicity that is grade 3 or greater should prompt the immediate discontinuation of study drug. A MedWatch is required for any hospitalization and any reportable toxicities per Guidelines in section 14.1.

4.4 Treatment Schedule

Study treatment will consist of donepezil and placebo. The donepezil will be dispensed as a single oral 5 mg tablet; placebo will be matched. The dosage for donepezil will be 5 mg or placebo, (one tablet) each evening for 6 weeks. If tolerated, the dose will then be increased to 10 mg Donepezil or placebo (two tablets) each evening for the remainder of the study.

4.5 Pre-Medication - N/A

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In the absence of treatment delays due to adverse event(s), treatment may continue for 24 weeks or until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.7 Concomitant Treatment

Patient must not have any planned therapy, including surgery, brain radiation of any type, chemotherapy, or immunotherapy during the next 30 weeks for brain or extracranial primary metastatic disease.

4.7.1 Many patients who have been treated for a primary or metastatic brain tumor will be on steroids. The patient should be maintained on the lowest steroid dose possible. Steroid tapers should occur as if the patient were not taking the study medication.

4.8 Supportive Care Guidelines: N/A**4.9 Patient Refuses Further Active Treatment**

Refusing active treatment may not necessarily mean the patient withdraws consent. If a patient refuses active protocol treatment after therapy begins, the data collection may continue according to protocol unless the patient also withdraws the consent in writing (to the site PI) which would then discontinue follow-up.

If patient discontinues protocol treatment, clearly indicate this on the flow sheet. Also, continue to follow patient on study and submit all patient completed data management forms. Contact DMC at (336) 713-3172 for any questions.

5. RADIATION THERAPY: N/A**6. SURGERY: N/A****7. OTHER THERAPY: N/A****8. PATHOLOGY/TISSUE BANK: N/A****9. PROTOCOL SPECIFIC TRAINING REQUIREMENTS:****9.1 Certification Requirement**

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All assessments will be conducted by trained and certified research personnel. Certification procedure must be completed by staff prior to patient enrollment. See Appendix 11 for certification requirements.

9.2 Certification Procedures

Certification for the administration of the neurocognitive battery and questionnaires will include didactic presentations, role-played administrations with Q&A and feedback. All training will be supervised by experienced test administrators (Dr. Rapp at WFUSM, June Fletcher-Steede, Site Coordinator) who will be responsible for certifying test administrators. They will also be responsible for helping staff maintain certification by having regular meetings to discuss the procedures and providing supplemental training as needed. See Appendix 11 for certification requirements.

10. CORRELATIVE/SPECIAL STUDIES: N/A

11. STUDY PARAMETERS

	Baseline	Wk 6	Wk 12	Wk 24
Informed consent	X			
Demographics	X			
Performance status	X		X	X
Brain MRI (B)	X			
Serum pregnancy test (A)	X			
Flow Sheet/Toxicity Assessment	X	X	X	X
Telephone Contact Form(C)		X		
Patient Survey Form	X			
Current Medication Form	X	X	X	X
Baseline Booklet	X			
12 Week Booklet			X	
24 Week Booklet				X
Pill Count (monthly & each visit)		X	X	X

A– Serum negative pregnancy test is required in women of child-bearing potential within 10 days of registration.

B – Brain MRI Report and CD – Required within histology parameters (Appendix 16) prior to registration. MRI must be obtained with and without contrast. Submit invoice for MRI CD to Attn. Gina Enevold, MSN, 2000 West First Street, Suite 401, Winston Salem, NC 27104

C - Phone interview for assessment of toxicities: if indicated, increase donepezil or placebo to 10mg/day starting week 7.

12. REGISTRATION PROCEDURES

A form 310 or IRB letter of approval and an IRB approved consent form must be received by the Research Base Protocol Information Office – Attn: Site Coordinator prior to patient registration. Fax: (336)716-6275

Fill out Appendix 2, “Eligibility Checklist / Registration Form’. Use this to complete the on-line registration.

Log on to the CCCWFU Research Base registration web site at <http://www.phsapps.wfubmc.edu/CCRBIS/Login/defaultlogin.cfm>>. Enter your user name and

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password (which may be obtained by contacting Ping Tan at ptan@wfubmc.edu or June Fletcher-Steede at jsteede@wfubmc.edu.) *In the 'Patient Registration and Protocol Information' table, click the 'Register Patient/Patient Info', with the corresponding protocol number found in the drop down box to the right. Fill in the eligibility criteria forms using the drop down boxes.* If further information is needed by Biologics or Data Management, they will contact you. Once the patient information has been entered online print a copy of the eligibility checklist/registration form for your records. Press the submit button, a confirmation page will appear. **Print this confirmation sheet for your records.** The CCCWFU On-line Protocol Registration/Eligibility form, initial flow sheet, signed consent, histology reports, scan reports and lab reports (as required in protocol) should be faxed to 336-713-6476 or mailed to Data Management:

Research Base Data Management Center
Department of Radiation Oncology
1st Floor Cancer Center
WFUBMC
Medical Center Boulevard
Winston-Salem, NC 27157

These forms should be retained in the patient's study file. These forms will be evaluated during an institutional NCI/CCCWFU CCOP Research Base site member audit.

If you have questions related to the registration process or require assistance with registration, please contact the CCCWFU CCOP Research Base DMC between 8:30am and 4:00pm EST, Monday through Friday at (336) 713-6507.

CTSU Participants: Refer to the CTSU Logistical Appendix 17 for site registration and patient enrollment instructions.

13. DATA SUBMISSION PROCEDURES

The Eligibility Checklist/Registration Form should be completed online prior to placing the patient on study. Data forms will be submitted to the CCCWFU CCOP Research Base, Attn: Data Management Center, Outpatient Comprehensive Cancer Center, Medical Center Boulevard, Winston-Salem, NC 27157-1030 according to the timetable below:

Form	Submission Schedule
Baseline CD of Brain MRI*	At Baseline
Eligibility Checklist/Registration Form	Upon Registration
Informed Consent	Upon Registration
Flow Sheet and Toxicity Assessment	Upon Registration within 2 weeks of 6, 12, 24 week visit
Neurocognitive Booklets	<ul style="list-style-type: none"> • Baseline Booklet within 2 weeks of Baseline visit • 12 week Booklet within 2 weeks of 12 week visit • 24 week Booklet within 2 weeks of 24 week visit
Patient Survey Form	Baseline
Telephone Contact Form	Within 2 weeks of 6 week phone contact
Medication Diary (Pill count)	Monthly and each visit (6, 12, 24 week)
Current Medication Form	Baseline, within 2 weeks of 6, 12 & 24 week visit

*Submit invoice for MRI CD to Attn. Gina Enevold, MSN, 2000 West First Street, Suite 401, Winston Salem, NC 27104

14. ADVERSE EVENT REPORTING

Federal regulations require that investigators report adverse events and reactions in a timely manner.

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14.1 Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at the beginning of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to the beginning of treatment or an event though present at the beginning of treatment becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

Known/expected events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

- Definite - The adverse event *is clearly related* to the treatment/procedure.
- Probable - The adverse event *is likely related* to the treatment /procedure.
- Possible - The adverse event *may be related* to the treatment/procedure.
- Unlikely - The adverse event *is doubtfully related* to the treatment/procedure.
- Unrelated - The adverse event *is clearly NOT related* to the treatment/procedure.

14.2 Grading Of Adverse Events

Unless specified otherwise, the NCI Common toxicity Criteria (CTC) v3.0 is used to grade severity of adverse events for this protocol.

- Grade 1 - Mild AE
- Grade 2 - Moderate AE
- Grade 3 - Severe AE
- Grade 4 - Life-Threatening or disabling AE
- Grade 5 - Death related to AE

14.3 General Guidelines

In order to assure complete and timely reporting of adverse events and toxicity, the following general guidelines are to be observed. When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supersede the General Guidelines. A protocol may stipulate that specific grade 4 events attributable to treatment are expected and may not require the standard reporting, however, exceptions to standard reporting must be specified in the text of the protocol.

Adverse Event reporting begins after the patient is registered to the study drug (or begins the run-in period of the study or begins the wash out period of the study). Adverse Events occurring within 30 days of study completion must be reported via FDA form 3500 (MedWatch).

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1. The protocol Principal Investigator will report to the RB Data Management Staff within 24 hours of discovering the details of all unexpected severe, life-threatening (grade 4) and fatal adverse events (grade 5) if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.
2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require notification within 24 hours of discovery.
3. Any medical event which precipitates hospitalization or prolongation of existing hospitalization, must be reported regardless of attribution or whether the adverse event is expected or unexpected.
4. A written report, including all relevant clinical information and all data collection forms due up to and including the date of the event will be sent by mail or FAX to the RB DMC within 10 calendar days unless specified otherwise within the protocol. The material must be labeled: "Attention: Adverse Event Reporting".
5. The Research Base Grant PI, Clinical Research Oversight Committee 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 warranted.
6. Serious adverse events will be communicated by phone and MedWatch as soon as identified to the CCCWFU Research Base Data Management Center (DMC) at (336) 713-4390. The DMC is responsible for communicating with the FDA, the drug sponsor, WFU IRB, and other regulatory agencies, as well as reporting all SAE's grade 4 or 5 to the Clinical Research Oversight Committee (CROC).
7. For events that require telephone reporting to the NCI, Investigational Drug Branch, the FDA or study sponsor, the investigator may first call the Research Base DMC unless this will unduly delay the required notification process.
8. A copy of all correspondences sent recipients of the notification, e.g. NCI, IDB, FDA must be submitted to the Research Base DMC. Copies must include the RB study and case (PID #).
9. Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All MedWatch reports should be sent to the local IRB in accordance with the local IRB policies.
10. When submitting AE, SAE reports and supporting documentation, the study number and the case number (PID #) must be recorded on the FDA Form 3500 (MedWatch) so that the case may be associated with the appropriate study file.

14.4 **Cancer Prevention Agents – Commercially available**

Cancer Prevention Study agents may or may not be commercially available, may or may not be sponsored by a third party and may or may not be under an IND. Adverse Event Reporting for all commercially available drugs should be reported via the FDA Form 3500 (MedWatch).

14.5 **Cancer Prevention Agents Supplied by NCI – N/A**

Table A: Adverse Events occurring within 30 days of study completion must be reported via MedWatch

	MILD				MODERATE				SEVERE			
	1		1		2		2		3		3	
	Unexpected		Expected		Unexpected		Expected		Unexpected		Expected	
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days
Possible Probable Definite	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days

	LIFE-THREATENING/DISABLING				DEATH			
	4		4		5		5	
	Unexpected		Expected		Unexpected		Expected	
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization
Unrelated Unlikely	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days
Possible Probable Definite	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days

CTEP, NCI Guidelines

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14.6 Unblinding Guidelines

In the event a patient on this study develops a life-threatening toxicity or serious adverse event for which the patient's physician or other health care professional feels that it is in the patient's best interest to know what drug they are taking (active study drug(s) or placebo), the following procedure should be followed:

- Step 1: the patient's physician or a designated health care professional should call the Wake Forest University Baptist Medical Center Physician Access Line (336-716-7654) and ask that Dr. Ed Shaw, Co-Principal Investigator of the CCCWFU CCOP Research Base, be contacted immediately either in his office, by pager, or at home. In the event Dr. Shaw cannot be reached, the PAL operator should contact Dr. Glenn Lesser, Chair, Cancer Treatment Protocols in his office, by pager, or at home. If neither Dr. Shaw nor Dr. Lesser can be reached, the PAL operator should contact Gina Enevold, Research Base Administrator, either in her office, by pager, or at home.
- Step 2: Once contact has been made; the patient's physician or health care professional should explain the reason for the request to unblind the treatment arm that the patient is on. If the Research Base representative feels that the toxicity (AE/SAE) is possibly, probably or definitely related to the study drug, then the next step will be followed.
- Step 3: The responsible Research Base representative will call the pharmacist @ Biologics, Inc.(phone: 1-800-850-4306). There is an "on-call" service provided 24 hours a day, seven days a week for the Chemical Drug Trials unblinding service. The Biologics pharmacist may contact the patients' physician and/or health care professional directly with the unblinding information. Written documentations of the unblinding process will be sent to the Research Base Principal Investigator by Biologics, Inc.

OR-

The responsible Research Base representative will locate the envelope which contains the code for all CCCWFU CCOP Research Base clinical trials which are double-blind. It is located in the Outpatient Comprehensive Cancer Center, Department of Radiation Oncology (first floor)in the Research Base Clinical Trials Office (phone: 336-713-6519), in a locked file cabinet drawer which bares the label "Unblinding Code". Only Dr. Shaw, Dr. Lesser, Ms. Enevold, and the Research Base Biostatistician (who maintains the unblinding code envelope for the appropriate Research Base trials) have a copy of the key.

- Step 4: In the event that the patient's treatment is unblinded, that patient will be taken off study with no further study follow-up. Appropriate procedures for grading toxicities, assigning causality, and reporting severe adverse events (if applicable), should be followed for each protocol for all Phase III Clinical Trials. The event will be reviewed by the CCCWFU Clinical Research Oversight Committee. All Phase III Clinical Trials will be reviewed by the CCOP Research Base Data Safety and Monitoring Board.

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The CCCWFU CCOP Research Base Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS)

15.0 STATISTICAL CONSIDERATIONS**15.1 Study Design**

In order to address the Specific Aims of this proposal, we propose to use a 24-week 2-arm double-blind randomized clinical trial to compare the effects of donepezil versus placebo on a series of cognitive, mood, and quality of life outcomes in long-term (>6 month) survivors of partial or whole brain irradiation. In order to guarantee balance of treatment assignment across the CCOP Research Sites, randomization will occur stratified by site.

15.2 Statistical Considerations/Analysis:

To test these hypotheses we will use a mixed model approach to compare the donepezil and control groups at 24 weeks after adjusting for baseline values of the outcomes. Additional covariates will be included in the models to accomplish one of two goals (or both): 1) to reduce bias that may exist in estimating treatment effects if the groups are unbalanced on covariates at baseline and 2) to increase precision of treatment effect estimates by controlling for covariates that are associated with the outcome of interest. After we fit the initial models, we will next examine patient characteristics measured at baseline such as age, gender, education level, race, and SES and include them in the model if they are found to be unbalanced between the groups. T-tests (for continuous covariates) and chi-squared tests (for categorical covariates) will be used to determine whether there is an imbalance between groups at baseline. Next, baseline assessments of variables such as fatigue, depression, radiation dose (total, dose per fraction, isodose curves), time since radiation, tumor location (R/L, lobes), maximum diameter enhancing tumor, maximum diameter peritumoral edema, presence of white matter changes, and presence of atrophy will be compared between groups to check for balance. In addition, these variables will be examined in a step-wise fashion and entered into the model if found to be significant predictors of the outcome measure so that we will maintain a parsimonious model. Once the set of covariates is determined, we will test for interactions between donepezil and the covariates to determine whether the donepezil effect is consistent across different subgroups. If interactions are found to be significant then stratified analyses will be performed based on these characteristics (although this is not anticipated to occur). Next, we will fit a repeated measures mixed model that incorporates the week 13 outcome measurements into the model. For the repeated measures analyses the mixed models approach that will be able to test the donepezil effect while appropriately controlling for within and between subject variability. When we develop the models we will determine whether the assumptions of general linear models are satisfied. Diagnostics and residual plots will be reviewed to ensure that the assumptions are met. Should assumptions be violated, transformations of the outcome data will be considered, where the order of the priority in choosing a transformation will be to satisfy the (1) linearity assumption, (2) homogeneity assumption (homoscedasticity), and (3) normality assumption.

In addition to the approach outlined above, we will consider analyzing our data using methods described by Meyers (9). In this approach, one derives a variable called the reliable change (RC) index for each outcome. This index is derived from the standard error of measurement (SEM). One advantage of this statistic is that the baseline level of

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performance of a given individual is accounted for, since these values may vary from patient to patient. The SEM is calculated from the test-retest reliability (r) and the standard

deviation of test scores (SD): $SEM = SD(1-r)^{1/2}$. The standard error of difference is then calculated: $SE_{diff} = [2(SEM^2)]^{1/2}$. A reliable change (RC) in test scores from baseline to follow-up is considered significant if it falls within a 90% confidence interval that does include zero. For each subject the difference between the pre-treatment baseline and each follow-up assessment will be coded (according to the RC index) as 1 (deterioration), 2 (no change), and 3 (improved). Cross tabulations between this variable, time, and possibly treatment group (to account for multi-arm studies) will be used to examine the percentages of patients in each treatment group that show meaningful losses or gains in the various test domains over the course of the study.

A disadvantage of using the RC approach, however, is that the magnitude of change is not captured however the mixed model approach described above does take this into account.

15.3 Power/Sample Size Consideration

We have designed this study to recruit 200 total patients (100 in each treatment (donepezil/control) arm). Based on previous experience with this patient population, we believe that at least 65% of these patients will return for their 24 week visit. Sample size and power calculations can be made based on direct comparisons between the expected changes in outcome means in the different treatment groups. These calculations need to account for the proportion of the variance in the outcome that is explained by the other terms in the model (i.e. baseline values). To adjust for the proportion of variance explained by the baseline measurements when estimating the variance for the follow-up outcome measure, we used the formula $[\Phi^2_{follow-up \text{ adjusted for baseline covariates}} = \Phi^2_{follow-up} (1-r^2)]$, where r^2 is the square of the correlation between the baseline and follow-up measure. Although our full models will incorporate the intermediate time point (12 week measurement) into the final analysis, our power calculation is based on examining the change in outcome from the baseline assessment until the end of the 24 weeks, thus r^2 above represents the correlation between the baseline assessment of the outcome of interest (i.e., POMS fatigue) and the follow-up assessment taken 24 weeks later. Therefore these power calculations will be conservative since the additional information provided by the intermediate (12 week) assessment of outcome measures is not included.

The following formula was used to describe the minimum detectable difference in terms of standard deviations between the donepezil and control groups:

$$\text{detectable difference (in SD units)} = \frac{\sqrt{2(1-r^2)(Z_{1-\alpha/2} + Z_{1-\beta})^2}}{\sqrt{n}}$$

In the above, r^2 is the percent of the variance of the follow-up outcome explained by the baseline measurements, $Z_{1-\alpha/2}$ is the value from the standard normal distribution corresponding to the alpha level chosen (1.96, which corresponds to alpha=0.05 [two sided]), $Z_{1-\beta}$ corresponds to the power chosen for the study (here 80% and 90%), and n corresponds to the total number of patients studied for the donepezil group. Using this formula, we examined the detectable differences for several possible sample sizes per group and determined that with 65 per group (Number expected to be available at 24 weeks if we recruit 100 per group) the detectable differences closely resembled what our previous work would indicate were clinically meaningful differences. Thus, the table below shows the detectable differences for different r and $Z_{1-\beta}$ values with n per group fixed at 65. Since our the mixed models to be fit to analyze this data will use all 100 participants baseline data

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these calculations should be conservative since the additional information provided at baseline should reduce the variability of these covariates. Based on our preliminary data, we found that the correlation, r , between baseline and 24 week measures was 0.13 for

POMS-Confusion, 0.70 for FACT-BR, Brain Symptoms Subscale, and 0.87 for the Composite Cognition score. Thus the table below shows the detectable differences for correlations approximately equal to those. The formula above gives us the detectable differences in terms of standard deviation units, however since we have preliminary data that provide estimates of standard deviations, the table below shows the detectable differences in the native units of the measurement of interest.

Outcome Variable	Observed Correlation	Observed Standard Deviation	Detectable Difference	
			80% Power	90% Power
FACT-BR, Brain Symptoms Subscale	0.70	10.9	3.82	4.42
POMS – Confusion	0.13	6.2	3.3	3.51
Composite Cognition Score	0.87	0.82	0.19	0.23

Based on the table above, we see we have 90% power to detect differences of 4.42 (FACT-BR, Brain Symptoms Subscale), 3.51 (POMS-Confusion), and 0.23 (Composite Cognition Score) if we were to observe correlations of 0.70, 0.13, and 0.87 between baseline and 24 weeks for each of these outcomes respectively. These correlations and detectable differences are all derived from the preliminary data we observed previously in the Phase II donepezil preliminary study. In our preliminary data, we observed a difference of 0.31 on the Cognition Composite score thus we believe we have sufficient power to detect this endpoint.

15.4 Missing Data Considerations

The primary analyses using a mixed model approach (PROC MIXED in SAS) will be performed first using only baseline and 24 week follow-up data. This model will include patients that drop-out prior to the completion of the trial. Next, a mixed model will be fit to include the 12 week assessments as well. The mixed models described above (including baseline and 24 week follow-up or baseline, 12 week, and 24 week follow-up) are flexible enough to include patients who drop out as long as the data that are missing are considered to be missing at random. If this assumption is met, we will have greater power to detect differences than described above since we will have larger samples to estimate both baseline and week 12 measurements and thus reduce the variability of these estimates. To be sure that missing at random assumption is met, we will examine whether there are specific baseline characteristics that predict certain patients to drop-out of the trial and if these characteristics are found then they will be used to adjust the treatment effect estimates. We may consider using more sophisticated statistical modeling to examine the missing data and may consider other methods too that have been suggested for make treatment effect comparisons in clinical trials in the presence of missing data. Dr. D'Agostino, our lead statistician for this proposal, has done extensive methodological research in the area of modeling data in the presence of missing data, and has developed methods that incorporate propensity score models in analyses to adjust for missing data. If needed, he will use these sophisticated approaches to handle the potential problems that may arise due to missing data.

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15.5 Power/Sample Size Considerations - QOL

Power calculations for this Aim are similar to those described in Aim 1. Based on our preliminary we found that the correlation, r , between baseline and 24 week measures was 0.70 for the POMS-total and 0.81 for the FACT-BR-Total. Thus the table below shows the detectable differences for correlations approximately equal to those.

Outcome Variable	Observed Correlation	Observed Standard Deviation	Detectable Difference	
			80% Power	90% Power
FACT-BR (Total)	0.81	23.6	6.80	7.87
POMS – Total	0.70	29.9	10.49	12.14

Based on the table above, we see we have 90% power to detect differences of 12.14 (POMS-Total) and 7.87 (FACT-BR-Total) if we were to observe correlations of 0.70 and 0.81 between baseline and 24 weeks for each of these outcomes, respectively. These correlations and detectable differences are all consistent with the preliminary data we observed previously in the donepezil pilot study.

15.6 Multiple Comparison Considerations

Since Aims 1 and 2 will be examining multiple end-points using the same scales, there could be some concern that an adjustment for multiple comparisons is needed when performing the analyses. Although we believe that each of the outcome measures described above are assessing unique characteristics that are affected by brain irradiation and will be improved by treatment with donepezil, we have still re-estimated detectable differences for each outcome using a very conservative Bonferroni approach for each aim. Essentially, we used an alpha of 0.0167 for Aim 1 (to account for 3 comparisons) and 0.025 for Aim 2 (to account for 2 comparisons). With this conservative approach, we can detect the following differences with 80% for each outcome: Composite Cognition Score (0.21), FACT-BR Brain Symptoms subscale (4.92), and (POMS-Confusion (3.69) for Aim 1 and POMS-Total (13.18), FACT-BR (8.55) for Aim 2). Each of these differences is less than that observed in our preliminary data from the donepezil pilot study, thus we believe we have adequate power to detect meaningful differences in this trial, even assuming a very conservative approach and multiple comparison adjustment.

15.7 Feasibility

The anticipated accrual is about 6 patients per month. Recruitment will occur at two primary sites, the Wake Forest University School of Medicine in Winston-Salem, NC and at the M.D. Anderson Cancer Center in Houston, Texas and at a total of six secondary community sites selected from their respective Community Clinical Oncology Programs. Each primary site will recruit 2 participants per month with secondary sites contributing a total of 2 additional participants. Accrual will take approximately 3 years. This is consistent with the accrual rate from the Phase II open label study of donepezil that was performed at Wake Forest from 2000-2003 (data presented in Preliminary Studies section of this grant application).

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15.8 Inclusion of Women and Minorities

Participants will be recruited from among English-speaking patients, male or female and independent of ethnicity or race, who are receiving care at the Comprehensive Cancer Center of Wake Forest University, MD Anderson Cancer Center, and their respective CCOP Research Bases. Exclusion from the study will not be made on the basis of gender, race or ethnicity. Both men and women and members of all ethnic groups are eligible for this trial. The proposed study population is illustrated in the table below.

Race/Ethnicity

Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male	87	10	5	1	2	100
Female	87	10	5	1	2	100
Total	174	20	10	2	4	200

Full text of the Policies, Guidelines, and Procedures pertinent to this section is available on the NIH web site (http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm)

15.9 Randomization Procedures

When patients are registered, they will be randomized to guarantee that the treatments are balanced for irradiation type (whole brain and partial brain). Within each cell defined by this variable (whole brain/ partial brain), we will use a randomized block procedure to assign patients to donepezil or control where the size of the block is variable (2 or 4). Thus, treatment balance will always be achieved after at most 4 or at least 2 patients. In addition to having the randomization stratified by irradiation type, stratification will also occur based on the two CCOP Research Bases.

All forms at the time of registration and follow-up must be faxed to: Clinical Research Management, Comprehensive Cancer Center of Wake Forest University, 336-713-6476. This includes the Protocol Registration Form, on-study and follow-up flow sheets, signed consent form, QOL test results, and cognitive function test results, conventional MRI reports and patient medication diary.

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