ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A221101

A PHASE III RANDOMIZED, DOUBLE-BLIND PLACEBO CONTROLLED STUDY OF ARMODAFINIL (NUVIGIL®) TO REDUCE CANCER-RELATED FATIGUE IN PATIENTS WITH HIGH GRADE GLIOMA

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Drug Availability
Drug Company Supplied: Armodafinil (Exempt IND 116927)

***Investigator having NCI responsibility for this protocol**
√Study contributor(s) not responsible for patient care.

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Participating NCTN Organizations
Alliance/Alliance for Clinical Trials in Oncology (lead)
ECOG ACRIN/ ECOG-ACRIN Medical Research Foundation, Inc
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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
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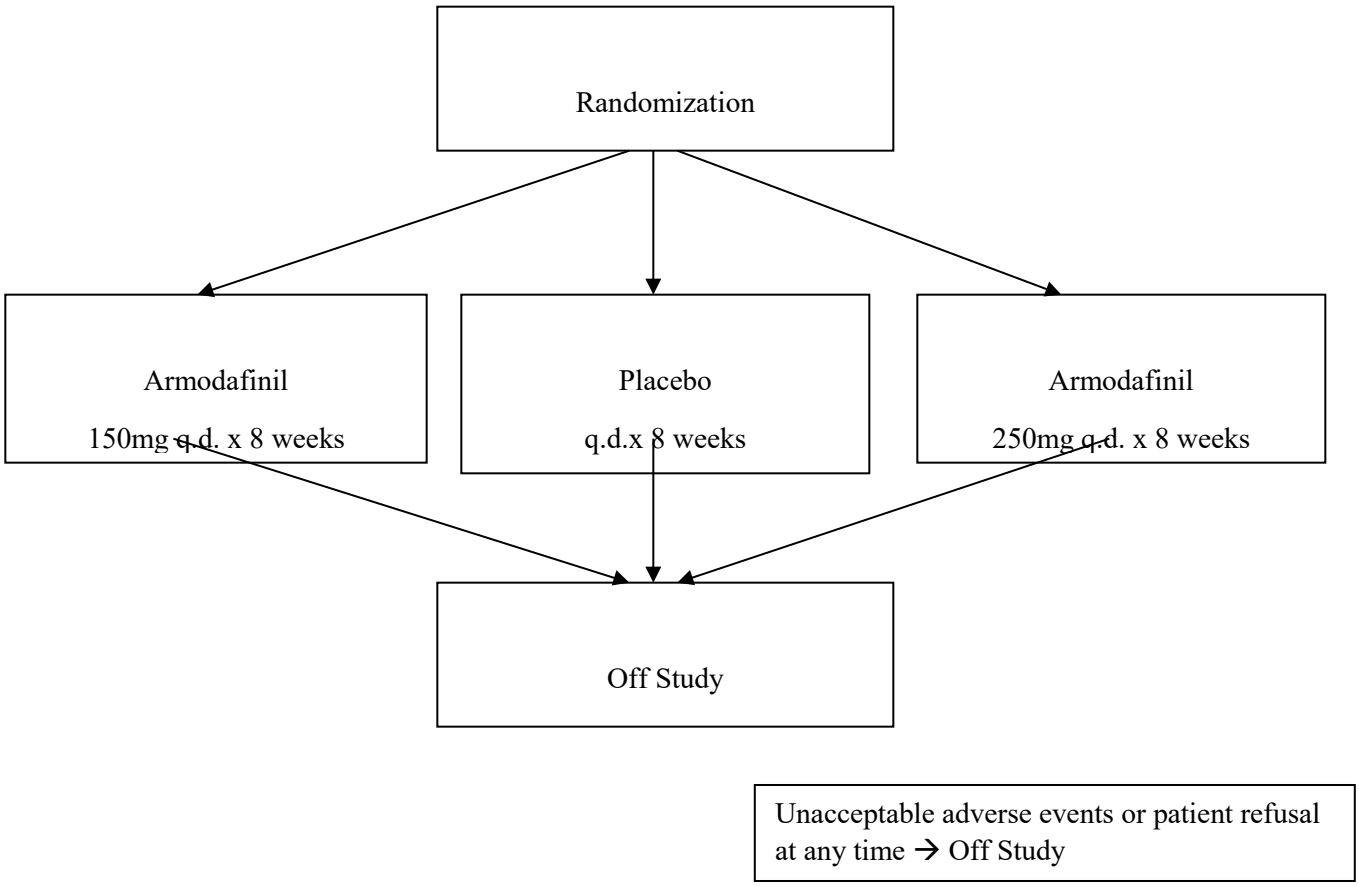
Schema



Cycle 1 length = 4 weeks
Cycle 2 length = 4 weeks

NOTE: Cycle is a data management tool to facilitate consistent remote data entry.

Generic name: Armodafinil Brand name(s): Nuvigil® Alliance Abbreviation: Availability: Alliance Research Base pharmacy	Generic name: Placebo Brand name(s): Alliance Abbreviation: Availability: Alliance Research Base pharmacy

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1.0 INTRODUCTION

1.1 Background

1.1.1 Fatigue is one of the most common and most troublesome symptoms for primary brain tumor patients throughout the disease trajectory (1, 2). This condition has long been under-recognized, under-diagnosed, and undertreated (3-6).

Cancer Related Fatigue (CRF) is a concerning issue in patients with cancer due to its high prevalence and negative effects on quality of life. Fatigue is a subjective experience. Sufferers may exhibit symptoms that are physical (physical weakness or tiredness), emotional (depression), motivational (lack of initiative or motivation), cognitive (impairment of cognitive function), and social (reduced ability to sustain social relationships) (7). In a survey evaluating Health-Related Quality of Life (HRQOL) in a variety of primary brain tumor patients at various times in the trajectory of their illness, 42% reported "quite a bit low" or "very low" energy levels (8,9).

Radiation therapy is the most common treatment modality for all brain tumor grades, and has been the treatment evaluated in the glioblastoma multiforme (GBM) patient population in relation to fatigue. Lovely and colleagues reported that over 80% of primary brain tumor patients report fatigue during radiation therapy (10). Fatigue has been reported to occur as early as within 1 week of the first radiation treatment and tends to increase with the number of radiation fractions (11). Fatigue which occurs during radiation therapy may continue into the post radiation period. Faithfull and Brada reported on the occurrence of a somnolence syndrome in the immediate post-radiation period (12). This syndrome included fatigue, excessive drowsiness, feeling clumsy, and an inability to concentrate. In this study, patients were followed during radiation and the immediate post-radiation period. Following completion of radiation therapy, the reported symptoms had a cyclical pattern, with increased severity between day 1-21 and then day 30-35 after treatment. Frequently, patients report that fatigue begins with treatment, continues during the course of treatment, and declines somewhat but persists at a higher-than-baseline rate after treatment is completed, sometimes lasting for months or even years (13-18).

Besides treatment factors, fatigue is often due to the tumor itself. The mechanism of direct tumor related fatigue is poorly understood and presumed to be a combination of the tumor biology itself, surrounding edema, and location. A prospective trial assessing quality of life in high-grade glioma patients found one third of patients had clinically significant fatigue at baseline before initiation of radiotherapy. In addition this study found fatigue to be an independent predictor of overall survival (19).

Clinically, a variety of other factors may contribute to the frequency and intensity of fatigue. These include concomitant medications such as chemotherapy, anticonvulsants, corticosteroids, metabolic disturbances, and psychosocial issues such as depression and anxiety. Most patients require corticosteroids to treat cerebral edema and anticonvulsants for seizure management. These medications have been reported to have a negative impact on fatigue in this patient population (11, 20). Recently, poor performance status, female gender, and active disease status were found to be associated with moderate to severe fatigue in patients with primary brain tumors (21). For males, antidepressants and opioids, in addition to performance status predicted fatigue severity (22). For women, variables that were most highly associated with fatigue severity were low-grade tumor diagnosis, steroids and active disease status (21).

1.1.2 Fatigue may also persist for years after diagnosis and completion of therapy.

A recent report explored the occurrence of fatigue in 58 patients with low-grade gliomas who were at least eight years from completion of tumor therapy (22). In this study, 39% of patients with a mean disease duration of 15 years, reported severe fatigue. Characteristics that differentiated those who were severely fatigued versus not severely fatigue included older age and anticonvulsant use (22).

There are limited studies to date exploring the occurrence and correlates of fatigue in patients with primary brain tumors. In patients with other solid tumors, fatigue is often the most common and severe symptom associated with the disease and treatment (22, 23). Fatigue has been demonstrated to cluster with other symptoms, including pain, distress, insomnia, and depression and influence outcomes such as perceived health and functional status (24-28). In the limited studies to date in patients with primary brain tumors, fatigue has been identified as a common symptom occurring in patients with both low and high grade tumors, to persist in long term survivors of low grade brain tumors, to be associated with both radiation and a variety of chemotherapies and to be more severe in women and in those with progressive disease.

1.1.3 Brain tumors and treatment are associated with cognitive dysfunction.

Normal cognitive functioning is the product of a complex interplay among multiple elements including attention span, learning and memory, visuospatial ability, mental flexibility, psychomotor activity and manual dexterity. The cholinergic neurotransmitter system is central for regulation of memory and learning, while the hippocampus is the primary region of the brain mediating cognitive function, primarily memory and attention. The basal forebrain is the major source of cholinergic innervation to the hippocampus. Derangement in any of these cognitive elements leads to a variety of cognitive and/or psychomotor problems which can range from hard-to-detect selective deficits to global impairments (28, 29).

The effects of cancer treatments on cognitive function have commanded increasing attention from researchers in the past decade (28-32). Cognitive deficits identified by cancer survivors consist of a range of difficulties including memory and concentration problems that can emerge during cancer treatment and/or months after completion (29). Cognitive deficits that occur as a result of cancer or its treatment vary widely and may be subtle or dramatic, temporary or permanent, and stable or progressive (33-36). Pathological evidence supports adverse effects of radiation on white matter tracts and cerebral vasculature of the brain secondary to damaged oligodendrocytes resulting in axonal demyelination, and, disruption of vascular endothelial cells contributing to coagulative necrosis, vessel wall thickening, and focal mineralization. Chronic radiation toxicity is also believed to involve alterations in neurogenesis as well as metabolic abnormalities and inflammatory responses (37-40).

Subtle cognitive changes pose unique challenges to detection and management. First, the cause of subtle changes in cognitive function may not be readily apparent, and the impairments may not be evaluable with standard, objective neuropsychological measures. Second, subtle changes in cognitive function may also be confused with or confounded by other problems commonly associated with cancer and its treatment, such as depression, anxiety, and fatigue.

Although the phenomenon is not understood completely, cognitive deficits in cancer patients are assuming greater significance as cancer survival improves. Advances in basic, imaging, and clinical sciences are beginning to unravel pathophysiologic mechanisms and

develop neuroprotective strategies. Conventional therapies soon may find new applications and pharmacologic options are borrowed from diverse diseases, including attention-deficit/hyperactivity disorder and neurodegenerative diseases.

1.2 Evidence-Based Interventions

The National Comprehensive Cancer Network (NCCN) has published clinical practice guidelines that encourage early identification and management of CRF during and after treatment (5).

Physical activity is first-line therapy for CRF. However, an exercise program should be initiated cautiously in patients who have neurologic deficits, are deconditioned or experiencing comorbidities such as bone metastases, myelosuppression, fever, or treatment-related complications (5). Structured exercise training has been associated with significant improvement in quality of life and improved fatigue across numerous cancer populations, however have not studied the effect of exercise among cancer patients with neurologic and/or cognitive deficits or those with glioblastoma (41). Jones and colleagues found that the six minute walking test was well correlated with KPS and QOL in patients with glioma. Their results then lead to the suggestion that interventions geared towards increasing their 6 minute walk timed test may cause considerable improvements in quality of life and fatigue in the recurrent glioblastoma patient population (42).

A lack of sufficient evidence precludes the routine use of pharmacologic therapy in patients with moderate-to-severe fatigue. However, the NCCN does list pharmacologic intervention with psychostimulants as an option in cases in which other causes of fatigue have been ruled out (5).

1.2.1 Clinical trials using methylphenidate for treatment of fatigue

Methylphenidate is a central nervous system stimulant similar to amphetamine with a short plasma half-life of 2 hours, a rapid onset of action, and duration of action of 3 to 6 hours (43). The baseline dose is usually 5 mg in the morning and at noon with titration as needed with a maximum dosing of 1 mg/kg/d. The most frequent side effects are tachycardia, nervousness, insomnia, and anorexia, especially at higher doses. Open-label studies suggest an improvement in fatigue (44, 45).

In a randomized controlled trial, 112 patients were assigned to 5 mg of methylphenidate or placebo and able to repeat dosing every 2 hours as needed to a maximum of 20 mg daily. At 7 days, significant improvement in fatigue compared to baseline was noted in both groups (46). The authors suggested that the observed benefits might be due to daily contact with the study nurse which may have had a major symptomatic or placebo effect.

A more recent study conducted by Moraska et al, reports the results of a randomized, controlled trial comparing methylphenidate versus a placebo in a group of heterogeneous group of patients with CRF (47). Adults who were eligible for this trial had to have a history of CRF as defined by a score of 4 or more on a subjective fatigue level screening scale that ranged from zero (none) to 10 (as bad as it can be), for at least 1 month before registration. The authors found no significant differences in usual fatigue, current fatigue or worse fatigue during the course of the 4 week study. The primary end point of prorated Area Under the Curve for the usual fatigue question of the BFI did not show a statistically significant difference between the methylphenidate and placebo arms (P=.32). The methylphenidate treatment arm demonstrated a 3.2% better fatigue score on average, which was16% the standard deviation of the fatigue scores (a small effect size) and not significantly different than that in the placebo arm. The authors did observe however, that patients with more advanced disease showed a significant response to methylphenidate as well as a trend for more improvement in usual fatigue for those who reported more severe fatigue at baseline with methylphenidate as opposed to placebo. This study excluded

patients with CNS malignancies, however. Similar results have also been reported by Yennurajalingam et al (48). They conclude that higher levels of fatigue were predictors of response to methylphenidate in patients with advanced cancer in a randomized clinical trial conducted at MD Anderson.

In terms of fatigue prevention, a phase III randomized, double blind study evaluating d-THREO-methylphenidate HCL (MPH) in patients with brain tumors receiving radiation therapy was not able to show a benefit for the MPH in preventing fatigue. At the end of brain RT, there was no significant difference between groups taking MPH or placebo on the mean fatigue subscale score of the FACIT-F (49). The adjusted least squares estimate of the Mean Fatigue Subscale Score was 33.7 for the d-MPH and 35.6 for the placebo arm ($p = 0.64$).

Methylphenidate has also been evaluated with respect to treating cognitive deficits in patients with brain tumors. The first report was published in 1995 (50), in the treatment of neurobehavioral slowing associated with cancer and cancer treatment. Weitzner and colleagues described the effects of the psychostimulant methylphenidate on three patients who had cognitive deficits that had been caused by primary brain tumors or accompanying radiotherapy. Methylphenidate was expected to act as an indirect agonist, causing release of catecholamines that would control attention and memory. Arousal, attention, initiation speed of tasks, and mood were all improved.

Subsequently, Meyers and colleagues evaluated methylphenidate in patients who had primary brain tumors and abnormal neuropsychological test scores. Mean test scores in several cognitive domains were significantly improved in the group of 26 patients, despite progressive disease and increasing radiation damage. There were also improvements in subjective cognitive functioning and mood (51).

Based on its mechanism of action, methylphenidate is associated with a variety of adverse effects. Nervousness is among the most common adverse effects noted with general methylphenidate use (52, 53), while appetite loss and abdominal pain have been noted in many controlled clinical studies using this drug (54). This was noted in the study conducted by Moraska et al (47), where patients in the methylphenidate group reported adverse effects, including nervousness and appetite loss, compared with those in the placebo arm. Decreased libido and shakiness have also been noted as adverse effects in a small percentage of participants in placebo-controlled methylphenidate studies. Because of the adverse effect profile seen, future evaluations of methylphenidate should take into account the risk-benefit ratio from the patient's perspective.

Due to the poor side effect profile, the lack of positive data, and the potential for abuse, making this agent a Schedule II controlled substance, we do not wish to pursue methylphenidate as an agent for fatigue improvement in our brain tumor population.

1.2.2 Clinical trials using modafinil for treatment of fatigue

Newer psychostimulants with better side effect profiles and less potential for abuse are now available. Modafinil is a unique wake-promoting agent. Preclinical studies indicate a mechanism of action which is distinct from that of amphetamine or methylphenidate. To compare the pharmacodynamic profiles of modafinil, methylphenidate, and placebo in humans, a double-blind Latin square crossover study was conducted in 24 male volunteers with a history of polysubstance abuse that included the stimulant cocaine. Each subject was given single oral doses of methylphenidate (45 mg or 90 mg), modafinil (200 mg, 400 mg or 800 mg) and placebo. Measures of subjective, behavioral, and physiological responses were evaluated at fixed intervals during 72h after each dosing occasion. Subjects

discriminated both modafinil and methylphenidate from placebo. Subjects liked the effects of both drugs. However, modafinil differed from methylphenidate in its lack of a significant response on the Amphetamine Scale of the Addiction Research Center Inventory. The profile of physiological effects for modafinil differed from methylphenidate in that it showed greater inhibition of observed and reported sleep, less facilitation of orthostatic tachycardia and less reduction of caloric intake. These findings are consistent with preclinical pharmacological data suggesting that modafinil is not an amphetamine-like agent (55).

In an open-label trial conducted to evaluate the benefit of modafinil in managing CRF, patients who had completed treatment for breast cancer (chemotherapy, chemotherapy and/or radiation therapy), received modafinil 200 mg daily for 1 month (56). Upon completion of treatment with modafinil, mean fatigue severity decreased from 6.9 to 3.7 (0-10 scale: 0 = fatigue not present and 10 = fatigue as bad as you can imagine). The mean rating on the patient-reported global effectiveness measured after therapy was 5.0 (with 1 = no benefit and 7 = great improvement). This benefit rating supports the finding that participants perceived an improvement in fatigue with the use of open label modafinil. Furthermore, 51% of the patients reported improvement in sleep and 51% reported less daytime drowsiness. Additional benefits reported by a majority of patients (>60%) included improvements in general activity, mood, walking ability, normal work ability, relations with other people, and enjoyment of life. Four patients withdrew from the study: 1 due to pregnancy and 3 due to "agitation" that developed after 1 week of treatment.

Morrow et al (57) conducted a second open-label trial of modafinil, with the same purpose as the previous trial, in women with breast cancer who experienced fatigue levels of 2 or more on the Brief Fatigue Inventory (0-10 scale, 0 = no fatigue and 10 = fatigue as bad as it can be) at least 1 month following completion of radiation therapy. Patients received modafinil 200 mg once daily for 1 month. Of the 82 women enrolled, 76 completed the study. Reasons for discontinuation were pregnancy (n = 1), anxiety (n = 2), headache (n = 2), and nausea (n = 1). Ninety percent of the women experienced an improvement in fatigue.

One of the limitations of these studies is the design (56, 57). As open-label trials, they are subject to bias from a lack of randomization, lack of blinding, and lack of a control arm. Furthermore, with availability of only the published abstracts that contain an abbreviated methods section, it is unclear what the full inclusion/exclusion criteria were. Likewise, the authors did not indicate whether patients were assessed and treated for other causes of CRF, and it is unknown whether patients received prior or concurrent treatment for this condition. Patients who had received multiple prior treatments or concurrent therapy, including exercise, may have suffered from a more severe form of CRF. Therefore, observing a benefit from modafinil in these patients would strengthen the support that the drug provides a positive effect.

Jean-Pierre et al have reported the results of a multi-center phase 3 randomized placebo-controlled double-blind trial of the effect of modafinil on CRF among 631 patients receiving chemotherapy (58). Patients who reported fatigue were randomly assigned to receive either 200 mg of oral modafinil daily or a matching placebo. Treatment began on Day 5 of Cycle 2 and ended after Day 7 of Cycle 4. Fatigue and depression were assessed during Cycles 2 to 4 by using psychometrically valid measures. Group differences (treatment vs. control) in the worst level of fatigue during the previous week at Cycle 4 were examined by using an analysis of covariance (ANCOVA) adjusting for baseline fatigue (Cycle 2). Patients reporting more severe fatigue (level >6 on a 10-point scale) at cycle 2 experienced greater improvement than patients reporting moderate or mild levels

(p = 0.017). Of the patients studied, 26 were noted to have a cancer primary other than GI, GU, breast, lung, gynecologic, or hematologic systems. The authors do not report whether or not these patients had CNS malignancies and if so, the exact type.

The authors conclude modafinil may be useful in controlling cancer-related fatigue in patients who present with severe fatigue but is not useful in patients with mild or moderate fatigue.

More directly related to the needs of patients with brain tumors, a randomized, dose-controlled trial was conducted to assess the safety and efficacy of modafinil in 30 patients with cerebral tumors suffering from neurobehavioral dysfunction and/or fatigue post-treatment (59), 8 (27%) with glioblastoma multiforme and 10 (33%) with anaplastic glioma. Unfortunately, to our knowledge the results of this study have not been published to date and therefore, besides the information reported in the abstract, we are unable to provide details on how large a study was conducted , whether it was blinded, used a placebo or how large the differences were between the active and control groups . Fatigue levels were reported at baseline, week 8, and week 12 using the Fatigue Severity Scale (FSS; score range 1-7, lower score indicates less fatigue), Visual Analog Fatigue Scale (VAFS; score range 0-10, higher score indicates less fatigue), and the Modified Fatigue Impact Scale (MFIS; score 0-84, lower score indicates less fatigue). At baseline, 43% of patients were suffering from marked attention/memory impairment and/or fatigue, while 47% were identified as having severe illness by the Clinical Global Impressions Severity Scale, which rates the severity of illness as normal, borderline, mild, moderate, marked, severe, or extreme. Patients had been previously treated with neurosurgical resection (93%), radiation (87%), and/or chemotherapy (70%). Improvements were seen in fatigue outcome measures, with the greatest improvements noted 8 weeks after baseline. There was little, if any, difference between scores achieved at 8 weeks and those reported at the end of the trial. The authors concluded that modafinil is effective in improving fatigue with a low incidence of adverse reactions. However, the rigor and specifics of this study cannot be evaluated.

Recent preclinical data suggest that modafinil (Provigil®) may have some cognitive enhancement capabilities as well. To our knowledge, the first study to address the effect of modafinil on cognition in patients with cancer was done by Kohli et al at the University of Rochester, NY. They found that 200 mg of modafinil given to patients who had been treated for breast cancer, helped improve patient accuracy and speed of retention. Patients treated with modafinil had improved verbal and visual memory storage, retrieval, and retention (60).

The efficacy of modafinil in treating cognitive dysfunction in patients receiving treatment for glioblastoma is unknown.

1.3 Mechanisms of Newer Psychostimulants and Rationale for Armodafinil (Nuvigil)

Modafinil is a central nervous system (CNS) stimulant approved by the Food and Drug Administration for the treatment of excessive sleepiness associated with narcolepsy, shift work sleep disorder, and obstructive sleep apnea (61, 62). Modafinil is theorized to cause neuronal activation in areas of the hypothalamus associated with normal wakefulness. This mechanism is unique from that of other centrally acting agents such as amphetamines, which cause widespread activation of the CNS. In comparison with other stimulants, modafinil has a low potential for abuse due to a lack of activity on dopamine receptors (6, 63). Important proposed differences between methylphenidate and modafinil are the primary effects on the cortical versus subcortical areas and the decrease in GABA, accompanied by adrenergic agonist effects; an increase in serotonin and histamine. Modafinil is generally well tolerated. Preliminary data demonstrate

benefits of modafinil use, with minimal toxicity and a low propensity for abuse, in patients who have received cancer treatment or are currently undergoing chemotherapy. The most frequent adverse events (5%) are headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia (61).

Armodafinil is the R-enantiomer of modafinil which is a mixture of the R- and S-enantiomers. Concentration-time profiles of the two enantiomers show the pure R-enantiomer to be the longer lasting of the two enantiomers (10-14 hrs vs, 3-4 hrs), with a longer elimination half-life than modafinil. The two medications are virtually identical clinically when adjusted for the 2 to 1 greater dose level for modafinil. The exact mechanism of action is unknown. Armodafinil belongs to a class of drugs known as eugeroics, which are stimulants that provide long-lasting mental arousal. Pharmacologically, armodafinil does not bind to or inhibit several receptors and enzymes potentially relevant for sleep/wake regulation. Armodafinil is not a direct- or indirect-acting dopamine receptor agonist. However, in vitro, both armodafinil and modafinil bind to the dopamine transporter and inhibit dopamine reuptake. The side effect profile of the two medications appears to be similar and a slight difference noted on the package inserts generally favor armodafinil.

While no studies to date have examined the benefits of armodafinil in reducing CRF, pharmacokinetic evidence suggests it will be at least the equivalent of modafinil in doing so. The precise mechanism(s) through which armodafinil (R-enantiomer) or modafinil (mixture of R- and S-enantiomers) promote wakefulness is unknown. Both armodafinil and modafinil have shown virtually identical pharmacological properties in nonclinical animal and in vitro studies (64) Data held at Cephalon Inc. and reported on by Darwish and colleagues (65) shows that the S- and R-isomers of modafinil exhibited similar inhibition of binding and functional activity at dopamine, norepinephrine and serotonin transporters. They also reported that while the two isomers of modafinil have approximately equipotent pharmacological activity, the S-isomer is eliminated rapidly, having a half-life of 4-5 hours, whereas the R-isomer has a half-life of approximately 15 hours. Essentially, modafinil is the S-isomer and armodafinil is the R-isomer.

A pharmacokinetic comparison of modafinil and armodafinil found that at steady state, armodafinil produces consistently higher plasma drug concentrations late in the day than modafinil when compared on a milligram to milligram basis (65). The different pharmacokinetic profile of armodafinil may result in improved usefulness throughout the day in patients compared with modafinil (66). In other words, due to the longer acting R-isomer, armodafinil may result in better control of fatigue for a longer time throughout the day.

Armodafinil is a novel psychostimulant that has shown promise as a cognitive enhancer in normal adults and patient populations, including schizophrenia and attention deficit hyperactivity disorder (67-70). Commonly prescribed to treat MS-related fatigue (67), armodafinil is also an alertness-promoting agent that reduces lapses of attention and vigilance that are caused by sleep deprivation and fatiguing disorders (71-73). Indeed, it has been suggested that the nootropic effects of armodafinil may be magnified among people with pronounced fatigue and pre-existing cognitive difficulties (74, 75). As cancer patients frequently suffer from significant fatigue and neuropsychological deficits, armodafinil has strong potential as a highly efficacious cognitive enhancer in this population. Despite this, no published studies have examined the use of armodafinil to treat fatigue or cognitive impairment in cancer patients.

Both armodafinil and modafinil have been well tolerated in patients with significant fatigue complaints. The adverse event profiles are similar between the two agents in head to head studies. At the highest dosage, headache was the greatest adverse event noted with use of armodafinil compared to modafinil followed by nausea and abdominal pain as the most frequently encountered adverse effects (76).

1.4 Study rationale

As modafinil and armodafinil are newer drugs, there remains a paucity of research specifically in cancer. However, data from other chronic illnesses that have symptoms of fatigue and cognitive impairment, as well as preliminary data with modafinil in patients with brain tumors (59), provides the impetus to study the newer psychostimulants in patients with high grade glioma. Although large RCT's with modafinil and methylphenidate have not shown a significant impact on fatigue (47, 58), these trials did not focus on, and often did not include, patients with brain tumors, specifically glioblastoma. These studies do provide data to hypothesize that patients with more severe fatigue (48, 58) may benefit from these agents. Although data to date do not support using methylphenidate during radiation treatment (49), newer psychostimulants with broader CNS effects still need to be evaluated for effects on fatigue during and after radiation therapy, specifically in brain tumor populations. There are two clinical trials currently actively recruiting patients that involve armodafinil. Both are using heterogeneous populations of people with brain tumors and both are using armodafinil during radiation therapy (77, 78).

We conducted an extensive literature search and could find no published data on the effects of 250mg of armodafinil in treating fatigue in brain tumor patients. Given the trend toward positivity of the studies ongoing with 150 mg dose (77,78) further investigation is needed to decipher if further benefit from a higher dose is plausible. The 250 mg dose of armodafinil has been proven safe and efficacious in a study that showed positive results in patients with narcolepsy (109). In addition, there are ongoing trials listed on clinicaltrials.gov using 250mg of armodafinil in patients with results pending. Our proposed three-arm study complements both of those trials and other ongoing studies (110) by evaluating armodafinil in a more homogeneous population, specifically high grade glioma, and evaluating armodafinil for its effects on severe fatigue once radiation therapy has been completed. Given that fatigue is prevalent at the completion of radiation therapy, this seems the best endpoint to evaluate. Cognitive difficulties are one of the elements of fatigue and hence, these two problems are sometimes difficult to tease apart. Fatigue measurement is more advanced than cognitive measurement, due to problems with practice effects for neuropsychiatric measures and the lack of understanding of how fatigue, sleep and mood impact cognition. Therefore, we believe that evaluating fatigue as the primary endpoint and cognition as a secondary endpoint is well justified.

2.0 GOALS

2.1 Primary

To determine preliminary efficacy measured by patient reported fatigue using the Brief Fatigue Inventory (BFI) at 8 weeks of two doses (150mg and 250mg) of armodafinil in treating moderate fatigue compared to placebo in patients with high grade glioma.

2.2 Secondary

2.2.1 To evaluate the tolerability at 8 weeks of 150mg and 250mg armodafinil in this patient population

2.2.2 To assess the effect of armodafinil at 8 weeks on cognitive function in patients with high grade glioma.

2.2.3 To assess the impact of armodafinil on global quality of life and other fatigue endpoints in this patient population with high grade glioma.

2.2.4 Explore the correlation between the BFI, PROMIS, and PRO-CTCAE measures, as well as, the relationship of fatigue and cognitive difficulties.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Age ≥ 18 years.

3.1.2 Diagnosed with glioblastoma, gliosarcoma, small cell or large cell glioblastoma, glioblastoma with oligo features, glioblastoma with primitive neuroectodermal tumor-like components (GBM-PNET) features, anaplastic astrocytoma, anaplastic oligodendroglioma, or anaplastic oligoastrocytoma who are clinically stable and have completed radiation therapy (excluding stereotactic radiosurgery) >21 days prior to registration. NOTE: Clinical stability will be defined as a stable or improved KPS compared to the prior month.

3.1.3 ≥ 6 score on the worst fatigue question of the BFI (Brief Fatigue Inventory, see appendix III Question 3). It is not required for the patient to complete the entire BFI to meet this criterion.

3.1.4 Undergone surgery (gross total or subtotal resection) or biopsy and will have been treated with concurrent radiation therapy and chemotherapy as standard of care for Glioblastoma, gliosarcoma, small cell or large cell glioblastoma, glioblastoma with oligo features, glioblastoma with primitive neuroectodermal tumor-like components (GBM-PNET) features, anaplastic astrocytoma, anaplastic oligodendroglioma, or anaplastic oligoastrocytoma patients. Note: radiation must be completed per Section 3.1.2, but chemotherapy is allowed.

Patients who are currently using Optune® device will be eligible to participate in this trial.

3.1.5 Negative serum pregnancy test done ≤ 7 days prior to registration only for women determined to be of childbearing potential by their treating physician**.**

3.1.6 Ability to complete questionnaire(s) by themselves or with assistance.

3.1.7 ECOG Performance Status (PS) of 0, 1, 2 or 3 (Appendix XV).

3.1.8 Provide informed written consent.

3.1.9 Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.1.10 Stable dose of corticosteroid ≥ 14 days prior to registration.

3.2 Exclusion Criteria

3.2.1 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.2.2 History of hypersensitivity to other psychostimulants.

3.2.3 History of steroid psychosis.

3.2.4 Currently taking medications for attention deficit hyperactivity disorder, history of or currently taking medications for severe anxiety disorder, schizophrenia, or

substance abuse by patient record and/or self-report. Note: Patients who had childhood ADHD and no longer require treatment will be eligible to participate.

3.2.5 Currently using any other pharmacologic agents or nonpharmacologic interventions to specifically treat fatigue, including psychostimulants, antidepressants, acupuncture, etc. will be excluded. Note: Antidepressants used to treat items other than fatigue (such as hot flashes or depression) are allowed if the patient has been on a stable dose for ≥ 30 days prior to registration and plans to continue for the duration of the trial.

Erythropoietin agents to treat anemia are allowed. Exercise is allowed.

3.2.6 Anticipating surgery

3.2.7 Uncontrolled hypothyroidism, **profound anemia** (hemoglobin level of <10 g/dL ≤ 28 days prior to registration), or **untreated clinical depression** per physician discretion. Patients with stable, controlled depression or receiving treatment for hypothyroidism will be eligible, if they have been on a stable dose for the past 30 days and plan to continue for the duration of the trial.

3.2.8 Any history of Tourrette's syndrome or tic disorder.

3.2.9 Any history of or active glaucoma.

3.2.10 Any history of intractable epilepsy.

3.2.11 Any of the following co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens:

- History of myocardial infarction
- Unstable angina
- Left ventricular hypertrophy
- Mitral valve prolapse syndrome

3.2.12 Receiving any medications or substances that are <u>strong or moderate inhibitors</u> of CYP3A4.

Use of the following strong or moderate inhibitors are prohibited ≤ 7 days prior to registration:

<u>Strong Inhibitors of CYP3A4:</u>

> 5-fold increase in the plasma AUC values or more than 80% decrease in clearance
Indinavir (Crixivan®)
Nelfinavir (Viracept®)
Atazanavir (Reyataz®)
Ritonavir (Norvir®)
Clarithromycin (Biaxin®, Biaxin XL®)
Itraconazole (Sporanox®)
Ketoconazole (Nizoral®)
Nefazodone (Serzone®)
Saquinivir (Fortovase®, Invirase®)
Telithromycin (Ketek®)

<u>Moderate Inhibitors of CYP3A4:</u>

> 2-fold increase in the plasma AUC values or 50-80% decrease in clearance
Aprepitant (Emend®)
Erythromycin (Erythrocin®, E.E.S. ®, Ery-Tab®, Eryc®, EryPed®, PCE®
Fluconazole (Diflucan®)
Grapefruit juice
Verapamil (Calan®, Calan SR®, Covera-HS®, Isoptin SR®, Verelan®, Verelan PM®)
Diltiazem (Cardizem®, Cardizem CD®, Cardizem LA®, Cardizem SR®, Cartia XT™, Dilacor XR®, Diltia XT®, Taztia XT™, Tiazac®)

3.2.13 Receiving any medications or substances that are inducers of CYP3A4.

Use of the following inducers are prohibited ≤ 7 days prior to registration

Inducers of CYP3A4:
Efavirenz (Sustiva®)
Nevirapine (Viramune®)
Carbamazepine (Carbatrol®, Epitol®, Equetro™, Tegretol®, Tegretol-XR®)
Modafinil (Provigil®)
Phenobarbital (Luminal®)
Phenytoin (Dilantin®, Phenytek®)
Pioglitazone (Actos®)
Rifabutin (Mycobutin®)
Rifampin (Rifadin®)
St. John's wort

4.0 TEST SCHEDULE

Test Schedule Table

	Active-Monitoring Phase			
	≤28 days prior to registration	**Baseline[6]**	**End of Week 4[7] (Cycle 1)**	**End of Week 8[7] (Cycle 2)**
General neurological exam, weight, performance status	X			
Pregnancy test	X[1]			
Performance status			X[4,5]	X[4,5]
Neurocognitive testing (Appendix VII)		X[3]	X[3,5]	X[3,5]
Adverse event assessment		X	X	X
Patient Questionnaire Booklet • Brief Fatigue Inventory (BFI) • PROMIS • PRO-CTCAE (for fatigue and cognition items) • Linear Analogue Self-Assessment (LASA) • FACT-Cog • Godin Leisure Time Exercise Questionnaire (GLTEQ) (Appendices III-VI, XIII, XIV)		X[2]	X[2,5]	X[2,5]
Nurse/CRA Phone Contact (Appendix XII)			X	X

1. If the treating physician determines that the woman is of childbearing potential, then a pregnancy test must be done ≤ 7 days prior to registration.
2. Patient questionnaire booklets **must** be used; copies are not acceptable for this submission.
3. Must be administered by credentialed personnel. See section 4.1 and appendices VIII and IX.
4. PS will be collected via the Nurse/CRA Phone Contact.
5. Administered at the end of weeks 4 and 8.
6. Baseline assessment must be done ≤ 14 days after registration and no more than 7 days prior to 1st day of study drug.
7. +/- 3 days, timing for week 4 and 8 assessments should be measured from time of study drug administration – not baseline.

4.1 Neurocognitive Testing

The 'Cognitive Testing' and 'Administration Procedures for the Neurocognitive Test Battery' are included in this protocol as Appendices VII and VIII, respectively. Booklets must be used for submission; copies of the appendices are not acceptable.

Note: Patients **may not** be registered to this study until at least one member from the site study team has received certification to perform neurocognitive testing.

4.1.1 Credentialing to Perform/Administer Neurocognitive Testing

Any individual member of a site study team who wishes to perform neurocognitive testing **is required to** be credentialed. Credentialing is specific to one individual person, it does not certify an entire study site or study team.

For all Alliance sites, the following must be completed prior to registering a patient. This study requires that the member of the study staff who will administer the neurocognitive testing to patients be credentialed by [redacted] **Each individual member of the study staff** who will be administering the neurocognitive testing must be credentialed.

Please order the "Neurocognitive Booklet for Certification Use Only" from the CTSU website (see Section 6.1.2) as the site prepares for IRB submission so the credentialing can be obtained prior to registering a patient.

4.1.1.1 Previously credentialed team members

Members of site study teams are considered partially credentialed to perform neurocognitive testing for this study if they have previously been credentialed for any one of the following studies: NCCTG N0577; BN001, CC001, CC003

Previously credentialed study team members will need to be partially re-certified for this study. Specifically, they need to do the following:

1. Review procedures for the Symbol Digit Modalities Test (see Section 11.2.1) and the A221101 neurocognitive training video for this test which is posted on the CTSU website. The Symbol Digit Modalities Test was not included in the aforementioned protocols.
2. Review Appendix VIII "Administration Procedures for Neurocognitive Testing" in the protocol, with special reference to the instructions for the Symbol Digit Modalities test.

   Note: Please have access to the Administration Procedures document while you view the brief A221101 neurocognitive testing training video for the Symbol Digit Modalities Test.

   Please allow enough time for the video to download. If you have difficulties downloading the video, please check with your institution's computer support/help desk first before contacting the protocol coordinator at the telephone number or email address listed on the Protocol Resource page of the protocol.
3. Obtain the "Neurocognitive Booklet for Certification Use Only" and complete the entire quiz.

4. Complete the practice test for Symbol Digit Modalities Test with a colleague (**not** a patient). You do not need to complete the practice portion for the other tests, just the Symbol Digit Modalities Test.
5. Please be certain to complete and sign the certification page of the booklet. Also, include the CTEP site code for every site at which a patient may be enrolled along with your email address.
6. Submit the entire booklet per section 4.1.1.3 below. Along with the booklet, be sure to include documentation of prior certification as follows: the name/number of the prior study and the approximate date of certification.

4.1.1.2 Not Previously credentialed team members

If not previously credentialed, the study team member(s) must complete the following process:

1. Review "Administration Procedures for Neurocognitive Testing" in Appendix VIII of this protocol and the A221101 neurocognitive testing training video posted on the CTSU website.

   Please have access to the Administration Procedures document while you view the A221101 neurocognitive testing training video.

   Please allow enough time for the video to download. If you have difficulties downloading the video, please check with your institution's computer support/help desk **first** before contacting the protocol coordinator at the telephone number or email address listed on the Protocol Resource page of the protocol.
2. Complete the "Neurocognitive Booklet for Certification Use Only." The booklet includes a brief quiz and a practice test. Complete the practice test with a colleague (not a patient).
3. Please be certain to complete and sign the certification page of the booklet. Also, include the CTEP site code for every site at which a patient may be enrolled along with your email address.
4. Submit the entire booklet per section 4.1.1.3 below.

4.1.1.3 Submitting certification booklets

Scan and email a copy of the entire booklet to [redacted] at [redacted]. OR

Mail to the following:

[redacted]

If mailing, be certain to keep a copy of the booklet at the site.

Emailing directly to [redacted] is the most efficient path to certification.

4.1.1.4 Team member certification review and confirmation

[redacted] will review the certification booklet. If there are concerns, she will call or email the member of the site study team to review. If there are no concerns, confirmation of the team member's certification will be emailed to the team member. The site should then submit the Certification Confirmation Form to CTSU per Sections 6.4.4 and 6.4.5.

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

4.1.2 Neurocognitive Tests Format

The credentialed site study team member will administer the neurocognitive tests to the patient using the patient questionnaire titled "Neurocognitive Examiners Booklet". On follow-up visits, it is preferred that patients complete the neurocognitive test battery **before** seeing the physician since the emotional impact of the results of their follow-up brain scan may influence the patient's performance on the neurocognitive assessments. The questionnaire booklet will take approximately 15 minutes to complete and includes the following tests:

a) Symbol Digit Modalities Test (Smith, 1982).

b) Controlled Oral Word Association.

c) Trail Making Test A and B (Reitan 1958).

4.1.3 Submission of the completed neurocognitive test questionnaires

The neurocognitive tests must be administered in the order stated to every patient at every visit per testing instructions (see Appendix VIII).

Note: For the 'Symbol Digit Modalities Test', DO NOT SCORE THIS TEST. Study staff administering this test should not make any corrections after the practice portion. Please leave it attached, make a copy for your records, and mail it still attached to the test booklet.

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

[redacted]

5.0 STRATIFICATION FACTORS

5.1 Concomitant Chemotherapy: Yes vs. No

5.2 Age: < 60 vs. ≥60

5.3 Corticosteroid use: Yes vs. No

5.4 Gender: Male vs. Female

Stratification factors will be age, gender, concomitant chemotherapy, and corticosteroid usage. Balance will be achieved through established randomization procedures, which balances the marginal distributions of the stratification factors (102). These dichotomous variables involve a total of 16 different level combinations of stratification factors which is well below the group sample size as recommended by Therneau (101). We will also include these covariates in the modeling processes specified in the statistical considerations.

6.0 REGISTRATION/RANDOMIZATION PROCEDURES

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

6.1 Registration Requirements

6.1.1 Informed consent:

The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

6.1.2 Ordering Questionnaires/Booklets

Neurocognitive certification and patient assessment questionnaire booklets for A221101 must be ordered prior to the registration of any patients. Site staff should obtain all necessary neurocognitive certification and patient assessment questionnaire booklets before registering patients. Booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A221101 website) and faxing the form to the CTSU data operations center at [redacted]. Samples of the booklets are found in Appendices III-VII, which are to be used for reference and IRB submission only. They are not to be used for patient completion. Note: The CTSU will not send questionnaire booklets until the site has submitted a copy of their IRB approval excerpt to the CTSU Regulatory Office.

6.2 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 [redacted]. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) [redacted]. Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/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 IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

Additional information can be found on the CTEP website at <[redacted]>. For questions, please contact the RCR ***Help Desk*** by email at [redacted]

6.3 Site Registration Requirements – IRB Approval

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

6.3.1 IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status

- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

6.3.2 In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually). If the necessary documentation is not submitted in advance of attempting patient randomization, the randomization will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

6.3.3 When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the CTSU is no longer necessary.

6.3.4 Downloading Site Registration Documents

Site registration forms may be downloaded from the A221101 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol # A221101
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements of A221101 site registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted).
- The Certification Confirmation Form received from Dr. Cerhan (see Section 4.1.1.)

6.3.5 Submitting Regulatory Documents:

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

Regulatory Submission Portal: [redacted] (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

6.3.6 Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

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

6.4 Patient Randomization

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

6.4.2 Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < [redacted] and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at [redacted] or from the OPEN tab on the CTSU members' side of the website at [redacted] To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

6.4.3 Prior to accessing OPEN, site staff must verify the following:

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

6.4.4 Access Requirements for Oncology Patient Enrollment Network (OPEN)

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.

- To perform randomizations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform randomizations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.
- To perform randomizations to trials accessed via the CTSU mechanism, you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at [redacted]. For any additional questions, contact the CTSU Help Desk at [redacted].

6.4.5 Treatment on this protocol must commence at the accruing membership under the supervision of an Alliance member physician.

6.4.6 Study participation cannot begin prior to registration and must begin within 14 days after registration.

6.4.7 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.4.8 Neurocognitive certification and neurocognitive patient testing questionnaire booklets must be used.

Copies of questionnaires in the appendices of this protocol are to be submitted to the local IRB for review and approval only and are not acceptable for data submission.

Note: Once the above conditions have been met, access the OPEN website and follow the instructions for enrollment.

The factors defined in Section 5.0, together with the registering membership, will be used as stratification factors. The values of the stratification factors will be recorded. The patient then will be assigned to one of the following treatment groups using the Pocock and Simon[65] dynamic allocation procedure which balances the marginal distributions of the stratification factors between the treatment groups.

- Armodafinil 150 mgs
- Placebo
- Armodafinil 250 mgs

6.5 Procedures for Double-Blinding the Treatment Assignment

To ensure that both the patient and the medical professionals who care for the patient are blinded to the identity of the treatment assignment, the below procedures must be followed.

6.5.1 Each patient will be assigned a bottle number at the time of registration. This number can be found on the confirmation of registration. After the site has registered/randomized their patient in OPEN and received an Alliance subject number, the site will need to fax a drug order form (Appendix XI) to the Mayo Pharmacy fax number [redacted]. The order form must include the patient's subject number, the assigned bottle number, the patient's initials, a complete shipping address, and the DEA Registration Number of the registering

investigator or the site's pharmacy. This must be done for every patient registration. The Alliance Registration Office personnel will also be notified when a patient is registered/randomized in OPEN. As a double check, the registration office will also notify the pharmacy of the registered patient and the assigned bottle number.

6.5.2 The number of the treatment bottle assigned to the patient will be recorded on the dosing form.

6.5.3 The treatment assignment will be Armodafinil or placebo. The dose will be prepared and labeled as "armodafinil OR placebo" so that the contents are not discernible to the individual administering the treatment.

7.0 PROTOCOL TREATMENT

7.1 Treatment Schedule

Agent	Dose Level	Route	Frequency
Armodafinil	150 mg (one tablet)	Oral	Every day in the morning for 8 weeks
Placebo	one tablet	Oral	Every day in the morning for 8 weeks
Armodafinil	250 mg (one tablet)	Oral	Every day in the morning for 8 weeks

7.2 Unblinding Procedures

Unblinding can be done only in cases of an emergency or at the time of study completion. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

7.2.1 Emergency Unblinding Procedures:

Unblinding can be done only in cases of an emergency or after the patient has completed protocol treatment. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling [redacted], pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., "A######")
- Alliance patient ID number (e.g., "999999")
- Patient initials (e.g., "L,FM")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation.

After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

7.2.2 Protocol-specified unblinding

Trial participants may be unblinded upon study completion. Contact the Alliance Registration Office at [redacted] during regular business hours. Upon confirmation by the Primary Statistician (or designee) that all study completion requirements have been met, the treatment assignment may be unblinded. No Alliance Executive Officer (or designee) approval is required.

8.0 DOSAGE MODIFICATION BASED ON ADVERSE EVENTS

The study medication dose should be stopped for any grade 3 or worse toxicities related to study agent, or at the patient's discretion regarding toxicity. Any of the above should be clearly recorded on the Adverse Event Form.

Patients can be discontinued abruptly (no need to taper).

9.0 ANCILLARY TREATMENT/SUPPORTIVE CARE

Patients who begin using any other pharmacologic agents or nonpharmacologic interventions after registration to specifically treat fatigue including psychostimulants, antidepressants, acupuncture, etc. will be taken off study.

Note: Antidepressants used to treat items other than fatigue (such as hot flashes or depression) are allowed if the patient has been on a stable dose for ≥ 28 days and plans to continue for the duration of the trial. Erythropoietin agents to treat anemia are allowed.

10.0 ADVERSE EVENT (AE) REPORTING AND MONITORING

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018. The CTCAE is available at [redacted]. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

10.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the test schedule in Section 4.0. For this trial, the Adverse Events forms are used for routine AE reporting (see Section 18.2 for adverse event form submission details).

10.2 CTCAE Routine Study Reporting Requirements

*** Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

10.3 Expedited adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the CTEP Adverse Event Reporting System (CTEP-AERS). In the rare occurrence when internet connectivity is lost, a 24-hour notification is to be made to the Alliance Central Protocol Operations Office. 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.

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 beginning April 1, 2018. 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: [redacted] All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

The Alliance requires investigators to route all expedited adverse event reports through the Alliance Central Protocol Operations Program Office for Alliance coordinated studies.

Be sure to read this entire protocol section, as requirements are described in both the table and bullet points following the table. Note that the additional instructions or exclusions are protocol specific, and in the case of a conflict, the additional instructions or exclusions supersede the table.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

10.3.1 Alliance A221101 Reporting Requirements

Expedited reporting requirements for adverse events that occur on studies under an IND/IDE ≤ 30 Days of the last administration of the investigational agent/intervention [1, 2]

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

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

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

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusions:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- Treatment expected adverse events include those listed in Section 15.0 and in the package insert
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.
- All new malignancies must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e., solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and in situ tumors.

  Secondary Malignancy:

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

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

  •Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])

  •Myelodysplastic syndrome (MDS)

  •Treatment-related secondary malignancy

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

Second Malignancy:

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

Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how it was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

- Pregnancy loss
  - Pregnancy loss is defined in CTCAE as "Death in utero."
  - Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
  - A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS recognizes this event as a patient death.
  - A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.
  - The reporting of adverse events described above is in addition to, and does not supplant, the reporting of adverse events as part of the reporting of the results of the clinical trial, e.g. routine reporting.

10.4 Contact Information for NCI Safety Reporting

Website for submitting expedited reports	[redacted]
AEMD Help Desk (for CTEP)*	[redacted] Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP trials	[redacted]
AEMD Help Email:	[redacted]
Technical (e.g., IT or computer issues ONLY) Help Phone*	[redacted]
CTEP-AERS Technical Help Email	[redacted]
CTCAE v4 Help/Questions Email	[redacted]
CTEP-AERS FAQs link	[redacted]
CTEP-AERS Computer Based Training link	[redacted]

Office phone and fax are accessible 24 hrs per day 7 days a week (The AEMD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.

10.5 Other Required Expedited Reporting

EVENT TYPE	REPORTING PROCEDURE
Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete a Notification Form: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the NCCTG Remote Data Entry System within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an CTEP-AERS report has been submitted, this form does not need to be submitted.

10.6 Adverse events to be graded at each evaluation.

Pretreatment symptoms/conditions are to be evaluated at baseline per CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event	Baseline	Each evaluation
Nervous System Disorder	**Headache**	X	X

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase.

11.0 TREATMENT EVALUATION

11.1 Patient Self-Report Measures

The Patient self-report measures will be given three times, baseline and after weeks 4 and 8 of treatment. These items together take approximately 20 - 25 minutes to complete.

Fatigue is measured by multiple approaches in this protocol to not only provide a complete description of the type of fatigue experienced throughout treatment by the patients but also to inform future studies as to the relative merit (reliability, validity, responsiveness) the alternative methods impart in measuring fatigue.

11.1.1 Brief Fatigue Inventory (BFI)

The BFI is a 9-item instrument that allows for the rapid assessment of fatigue level in cancer patients and identifies those patients with severe fatigue. Three items ask patients to rate their fatigue for "now," and fatigue at its "worst" and "usual" for the last 24 hours. The 11-point scales are bounded by 0 = "no fatigue" and 10 = "fatigue as bad as you can imagine." Using the same type of scales, the remaining questions ask patients to rate how their fatigue interferes with several quality of life domains including general activity, walking, mood, work, and relations with others. These scales are bounded by 0 = "does not interfere" and 10 = interferes completely." The reliability and validity of the BFI were demonstrated in a study of 305 cancer patients and 290 community-dwelling adults. An internal consistency coefficient (Cronbach's alpha) = 0.96 was demonstrated when the BFI was administered to 305 patients with cancer (80). The BFI has been demonstrated as viable primary endpoints for numerous cancer clinical trials and has been translated into 22 different languages (81).

Single-question assessment is the most commonly used and the most useful methodology. A score of 1–3 indicates the presence of mild fatigue that does not require clinical intervention, and scores of 4–6 and 7–10 indicate moderate and severe fatigue, respectively, which require further evaluation and clinical intervention (82).

11.1.2 PROMIS

The PROMIS fatigue short form is a 7-item assessment using 5 response categories similar to the initial FACT series of measures. It produces a single summated score for fatigue (91). It was recently endorsed by the NCI SxQOL Steering Committee for use in NCI-sponsored cancer control trials. It produces a single summative score for the purposes of analysis.

The PROMIS measure will be used mostly as an exploratory secondary measure. We will look at its psychometric properties with the population in this study and also look at concurrent validity using the BFI as a gold standard. There are two domains represented by the 7 items in the PROMIS fatigue short form; impact and experience. In an exploratory manner, these will be evaluated as subscales but also the scale will be evaluated as a unidimensional measure. Since the fatigue items have not been, to our knowledge, psychometrically validated in cancer populations, we do see the use of PROMIS fatigue as an exploration. Since there is a desire to use a core set of measures in fatigue studies going forward and PROMIS has been cited as being a logical set of measures to use in this regard, we felt it was important to include these and begin generating some psychometric data, particularly in this, more rare population of high grade glioma patients.

11.1.3 PRO-CTCAE

PRO-CTCAE Symptomatic adverse events (AE) in cancer trials are reported by clinicians using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE). To integrate the patient perspective into AE reporting, NCI contracted (HHSN261201000043C) to create a patient-reported outcomes companion tool (PRO-CTCAE). The validity and reliability of PRO-CTCAE's 124 items reflecting 78 symptomatic AEs is presently underway. The items being created and validated are intended to be complementary to existing symptom items in the NCI's Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE is an existing lexicon of clinician-reported adverse event items required for use in all NCI-sponsored trials. The goal of developing patient versions of CTCAE symptom items is to improve the accuracy and precision of adverse symptom assessment in cancer trials, and to bring the CTCAE into harmony with other areas of clinical research in which the gold standard for symptom evaluation is patient self-reporting. Information gathered through the PRO-CTCAE is intended to provide clinicians with more comprehensive information about the patient experience with treatment when trials are completed and reported. We are including six items from the PRO-CTCAE in this study for fatigue and cognitive function to provide further evidence of their reliability and validity and compare the PRO-CTCAE items to the other methods for assessing fatigue and cognitive function.

11.1.4 LASA

Linear Analogue Self-Assessment (LASA) items have been validated as general measures of global QOL dimensional constructs in numerous settings (83-88). A series of five LASA items have been constructed and validated at Mayo for use in cancer patients (89). The 5 aspects measured will be global QOL, physical, emotional, spiritual, and intellectual well-being. Dr. Sloan and colleagues have done extensive research on the application of single-item LASA measures for assessing a wide variety of PROs including fatigue, peripheral neuropathy, hot flash activity, and anxiety. These single-item assessments have become the most-used assessment in all NCI-sponsored cancer control studies (90). As a result of recent research, this study includes LASA measures for global QOL and fatigue and will include these measures in all future phase II and phase III clinical trials as an independent prognostic factor independent of performance status.

11.1.5 FACT-Cog (Secondary Cognitive Endpoint)

Patients in this study will self-report their perceived cognitive functioning using the FACT-Cog version 3 (92). For many cancer-related symptoms, given their subjective nature, self-report is the only way an assessment can be conducted. The FACT-Cog is a useful measure of perceived cognitive deficits and related quality of life for adults undergoing chemotherapy, and is the first patient-reported outcomes measure to be developed and validated with a sample of cancer patients. The scale measures the frequency of positive and negative cognitive functioning events over the past seven days, based on self-report. The measure utilizes a five-point Likert-type scale (ranging from 0 = never to 4 = several times a day) to assess several different aspects of cognitive function. Lower scores are indicative of poorer perception of functioning. The FACT-Cog assesses a broad range of cognitive domains (not just those specifically related to work) and provides a multidimensional view of the cognitive deficits often experienced by patients with cancer.

11.1.6 Godin Leisure Time Exercise Questionnaire (GLTEQ).

The amount of leisure time spent in physical activity will be assessed using the Godin Leisure Time Exercise Questionnaire (GLTEQ) (103). The GLTEQ consists of two questions designed to assess the frequency within a typical 7 day week of mild, moderate, and strenuous exercise performed for a duration of at least 15 minutes during a participant's free time. The measure is easily administered and brief, with a retest coefficient of .62, a concurrent coefficient of .32 and an objective validity coefficient of .56 compared with CALTRAC accelerometry, estimated VO2 max and body composition (via hydrostatic weight).18 The GLTEQ has also been used successfully in populations of adult cancer patients (104-108).

11.2 Objective Cognitive Measures (Primary Cognitive Endpoint)

The neuropsychological battery proposed for this study overlaps with batteries used in numerous North Central Cancer Treatment Group (NCCTG) multi-center trials for studies in patients with CNS tumors without any problems or complications.

Clinicians and researchers must balance the often conflicting goals of obtaining valid PRO data while not burdening patients or interfering with the provision of care in a busy clinical setting. When surveyed about the preferred properties for an assessment battery for neurological and behavioral function, 191 experts in clinical and epidemiologic research reported it should be brief, precise, and easy to administer, score, and interpret (93).

The Symbol Digit Modalities Test (SDMT; Smith, 1982) is a measure of attention, visual tracking, and psychomotor speed. The task consists of a brief practice, followed by a 90-second test trial. Subjects are given a key in which 9 symbols are paired with each of the digits 1 through 9. Below the key is a grid in which a random series of the symbols appear above empty boxes. The task is to fill in the correct digit under each symbol, without skipping boxes, as quickly as possible for 90 seconds. This task has been found to be a particularly sensitive indicator of brain dysfunction (95).

11.2.1 Controlled Oral Word Association

This test requires subjects to generate words beginning with specified letters. A brief practice is followed by three 60-second trials using three different first-letter cues. This is a measure of processing speed and phonemic verbal fluency, and is a task widely used in neuropsychological assessment.

11.2.2 Trail Making Test

Trail Making is a two-part sequencing task which requires subjects to connect numbered dots in order (Part A) and then to connect dots alternating between numbers and letters (Part B). Score is time of completion, with each trial scored separately. Part A measures psychomotor speed, concentration, and visual scanning. Part B requires the cognitive functions required for Part A, with added recruitment of cognitive flexibility (executive function) (86). This test has a long history of use in clinical neuropsychology, and has been found to be very sensitive to brain dysfunction in general (96, 97).

12.0 DESCRIPTIVE FACTORS

None.

13.0 TREATMENT/FOLLOW–UP DECISION AT EVALUATION OF PATIENT

If the patient discontinues the study agent prior to 8 weeks, the patient will go off study.

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. If the patient never received treatment, on-study material must be submitted.

A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted.

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 BODY FLUID BIOSPECIMENS

Not Applicable

15.0 DRUG INFORMATION

15.1 Armodafinil (Nuvigil®) or placebo

15.1.1 Background

Armodafinil indicated as adjunctive therapy in the treatment of obstructive sleep apnea (OSA) and to improve wakefulness in patients with narcolepsy and shift work disorder (SWD). Armodafinil is the R-enantiomer of modafinil, which is a mixture of the R- and S-enantiomers. The precise mechanisms through which armodafinil and modafinil promote wakefulness are unknown. Both agents have shown similar pharmacologic properties in nonclinical animal and in vitro studies.

- At pharmacologically relevant concentrations, armodafinil does not bind to or inhibit several receptors and enzymes potentially relevant for sleep/wake regulation. Armodafinil is not a direct- or indirect-acting dopamine receptor agonist. Armodafinil has wake-promoting actions similar to sympathomimetic agents, but the pharmacologic profile is not identical to that of the sympathomimetic amines.
- Armodafinil has been classified as a Schedule IV controlled substance. Investigators who prescribe this agent must have an up-to-date Controlled Substance Registration Certificate. The agent must be stored in compliance with state and federal regulations related to Schedule IV controlled substances.

15.1.2 Formulation

Commercial armodafinil (Nuvigil®) tablets contain 50, 150 or 250 mg of armodafinil and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and pregelatinized starch.

15.1.3 Preparation and storage:

Armodafinil (Nuvigil®) tablets are stored at 20° to 25°C (68° to 77°F)

15.1.4 Administration:

Armodafinil will be taken as a single dose in the morning. Food delays absorption, but this has minimal effects on bioavailability. Armodafinil may therefore be taken without regard to food intake. If the patient misses a dose, the tablet can be taken that day as long as it is atleast 12 hours before the next dose.

15.1.5 Pharmacokinetic information:

a) Absorption – Readily absorbed.

b) Distribution –Vd: 42L. Approximately 60% protein bound, primarily to albumin (based on modafinil)

c) Metabolism –Hepatic, via multiple pathways, including CYP3A4/5. Metabolites include R-modafinil acid and modafinil sulfone. Clearance is 33 mL/minute, mainly via hepatic metabolism. Half-life elimination is 15 hours. Steady state is reached at approximately 7 days. The time to peak concentration (fasting) is 2 hours.

d) Excretion – Urinary (80%, predominantly as metabolites); < 10% as unchanged drug.

15.1.6 Potential Drug Interactions:

Armodafinil is a major substrate of CYP3A4. Dosage adjustment should be considered for concomitant medications that are substrates for CYP3A4/5, such as steroidal contraceptives, triazolam, and cyclosporine. Armodafinil is a moderate inhibitor of CYP2C19. Drugs that are largely eliminated via CYP2C19 metabolism, such as diazepam, propranolol, and phenytoin may have prolonged elimination upon coadministration with armodafinil, and may require dosage reduction and monitoring for toxicity.

15.1.7 Known potential toxicities

The use of armodafinil is contraindicated in patients with hypersensitivity to armodafinil, modafinil, or any component of the formulation.

Use is not recommended in patients with a history of angina, cardiac ischemia, recent history of MI, left ventricular hypertrophy, or patients with mitral valve prolapse, who have developed mitral valve prolapse syndrome with previous CNS stimulant use.

Angioedema and hypersensitivity (with rash, dysphagia, and bronchospasm) have been observed with armodafinil. Small average increases in mean systolic and diastolic blood pressure were seen in patients with narcolepsy taking armodafinil when compared to placebo.

Serious and life-threatening rashes including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms have been reported with modafinil, the racemate of armodafinil. Most cases have been reported within the first 5 weeks of therapy.

In pre-approval narcolepsy, OSA and SWD controlled trials of armodafinil, anxiety, agitation, nervousness, irritability, and depression were reasons for treatment

discontinuation more often than for placebo. Cases of suicide ideation were also observed in clinical trials.

The use of armodafinil may impair the ability to engage in potentially hazardous activities.

The agent should be administered at a reduced dose for patients with severe hepatic impairment. There is inadequate information to determine the safety and efficacy of dosing patients with severe renal impairment. Elimination of the agent and its metabolites may be reduced in elderly patients. Consideration should be given to the use of lower doses in this population.

Headaches are dose related and reported in > 10% of patients. Adverse reactions reported in 4 to 10% of patients include nausea (dose related), dizziness, insomnia (dose related), anxiety, and diarrhea. Adverse events reported in < 4% of patients include: depression (dose related), dyspepsia, fatigue, palpitations, rash (dose related), upper abdominal pain, agitation, anorexia, constipation, contact dermatitis, decreased appetite, depressed mood, attention disturbance, dyspnea hyperhidrosis,, increased heart rate, flu-like syndrome, loose stools, migraine, nervousness, pain, paresthesia, polyuria, pyrexia, thirst, tremor, xerostomia (dose related), and vomiting.

15.1.8 Study agent procurement

Armodafinil 150mg and 250mg tablets will be purchased for use in this trial. The placebo tablets will be purchased from PharmOps Inc. Armodafinil and placebo will be bottled, labeled, and distributed by the Alliance research base pharmacy. The armodafinil/placebo will be provided in bottles containing 56 tablets.

Each participating Alliance main membership or each participating affiliate site will order *one* patient-specific bottle of blinded armodafinil/placebo from the research base pharmacy each time a patient is registered in the trial. Fax the completed Alliance Clinical Drug Order/Return Form to:

See protocol Appendix XI for specific instructions.

Outdated or remaining drug/product should be destroyed on-site per procedures in place at each institution.

15.1.9 Nursing Guidelines

- Patients must take drug in the morning, with or without breakfast.
- Headaches are possibility. Instruct patients to contact study staff if they develop new onset of headaches.
- Instruct patient to monitor for hypersensitivity reactions such as rash and itching. Patients should immediately report any signs of fever, spreading rash, or joint aches.

15.2 Placebo

Placebo tablets will be purchased from PharmOps, Inc., Phillipsburg, NJ. The tablets will similar in appearance to the armodafinil tablets. The tablets will contain anhydrous lactose (bulking agent), microcrystalline cellulose (bulking agent/binder), crospovidone (disintegrant), and magnesium stearate (lubricant).

16.0 STATISTICAL CONSIDERATIONS AND METHODOLOGY

16.1 Study Design

This is a three-arm randomized clinical trial. The primary goal of this study is to compare the response rate of patients randomized to one of two doses of armodafinil or placebo in terms of a clinically meaningful improvement in patient-reported fatigue of at least a two-point improvement in the 0-10 point Brief Fatigue Inventory usual fatigue item at eight weeks post-treatment initiation. Endpoints will be assessed per arm and compared across arms by comparing each armodafinil arm versus the placebo arm in turn. We make no adjustment for multiple comparisons as we want to err on the side of moving forward the appropriate dose into phase III testing upon the basis of promising information in the proposed trial.

The three arm randomized trial will accrue a maximum of 330 patients to randomize a 100 evaluable patients per arm based on a binary endpoint to armodafinil or placebo.

Bayesian adaptive "shadow" design: Bayes clinical trial designs are becomingly increasingly more popular as alternatives to classic Fisherian designs, especially in the phase I context (110). They have not, however, been applied to cancer control cooperative group clinical trials. As a feasibility exercise, we will use the results of this trial to "shadow" what would have happened if the Bayes design would have been used. This will provide us insights into the relative utility of the Bayes design within the context of cooperative group cancer control clinical trials. The potential advantage of the Bayes approach is that the study likelihood of efficacy is constantly monitored allowing for the possibility of early study completion and therefore a smaller number of patients put at risk (see MD Anderson Cancer Center Technical Report UTMDABTR-002-06 (98). There are a number of logistical and statistical issues that were raised in the review of the concept (which initially proposed a Bayes design) that we decided it would be more prudent to use a classic Fisherian design to run the trial and use a shadow design to obtain preliminary data for planning future cancer control clinical trials using a Bayes approach. The details for the Bayes design are attached as Appendix X.

16.2 Sample Size

On average, we recruit six patients per month for GBM treatment trials. For symptom control studies with heterogeneous populations, such as N05C7 (Concerta), we were able to average 25 patients a month. We have found that symptom management trials targeting symptoms with a high prevalence have rapid accrual. Therefore, for this study, a reasonable conservative estimate for this more homogeneous population would be 8 patients a month. With 330 patients, accrual would be completed in 41 months.

The randomized design to be utilized is described below. Based on our previous work, we estimate that the response rate for the placebo arm will be 10%. We design the study with 100 patients per arm so that the Fisher's exact test will have 80% power to detect a response rate of 25% with a two-tailed alternative and a 5% Type I error rate for each treatment comparison to the placebo. Again, we are not using a conservative multiple contrasts approach because we want to err on the side of accepting a modest armodafinil effect. We plan to accrue an additional 30 patients to account for patient cancellations, ineligibility, or major treatment violations. Therefore, there will be a maximum of 330 patients accrued to this study unless undue adverse events are encountered.

16.3 Primary Endpoint

The primary endpoint of this trial is the response rate in terms of a clinically meaningful improvement in patient-reported fatigue at 8 weeks. A response is defined as an improvement of 2 points on the 0-10 scale of the usual fatigue on the BFI.

All patients meeting the eligibility criteria who have signed a consent form, have begun treatment, and have not had a major treatment violation within the 1st cycle of treatment will be evaluable for the primary endpoint. Patients will be analyzed according to the arm in which they were randomized.

Comparison of the primary endpoint between arms will be based on a binomial point estimate computed for each arm and a Fisher's exact test will be the inferential hypothesis test.

16.4 Secondary Endpoints

16.4.1 Other time points: The same analyses carried out using the 8 week assessment data will be used for analysis of data from the other time point assessments.

16.4.2 Other fatigue measures: The other fatigue items ("usual", "usual" and "now") as well as the impact of fatigue items from the BFI, the PRO-CTCAE, and the summated score from the PROMIS fatigue measure will be analyzed separately in turn comparing the average of these variables for each treatment using Kruskal-Wallis testing for change from baseline to four weeks, AUC over the entire treatment period, and repeated measures ANOVA using all treatments and all time points.

16.4.3 Cognitive function: The same analyses outlined for the other fatigue measures will be carried out for each of the cognitive function tests.

16.4.4 Quality of life: The same analytical approaches will be used to compare the three treatments in terms of QOL as was outlined for the other fatigue measures.

16.4.5 Safety and tolerability of armodafinil: Comparison of the proportion of patients reporting adverse events via the CTCAE items will be compared across treatment arms using a Fisher's exact test.

16.4.6 Area under the curve (AUC) and summary statistics: For the continuous measures mentioned above, AUC summary statistics will be generated for each patient to represent the overall experience reported by patients for each endpoint (e.g. fatigue) by combining the data from baseline, weeks 4, and 8 assessment points. The average of these AUC variables will be compared between the two treatment arms using two-sample t-tests. Further summary statistics will be constructed for the categorical variables to indicate whether the patient ever responded over the entire treatment period. These categorical variables will be compared between treatment groups via Fisher's exact tests.

16.4.7 Repeated measures analysis: The overall experimental layout will be examined via the construction of a repeated measures model using data from all assessment time points involving the continuous variables described above. Tests for time by treatment interaction will be carried out by the profile analysis methods of Srivastava. Covariates such as age, gender and other clinical variables may be included to test their impact on the initial efficacy tests of the primary and secondary analyses described above. Use of the Optune® device will also be included as a descriptive factor.

16.4.8 Logistic regression analysis: The overall experimental layout will be examined via the construction of a logistic regression model using the categorical response variables described above. This will allow for the characterization of the demographic and clinical variables' impact on the identification of a patient as a responder per the above definition.

16.5 Statistical Design

The primary endpoint for the trial is the response rate in terms of a clinically meaningful improvement in patient-reported fatigue, defined as at least a two-point improvement in fatigue as measured by the usual fatigue item from the Brief Fatigue Inventory at 8 weeks. This change

will be from baseline to 8 weeks (after randomization). The design proposed for this study will randomize a maximum of 330 evaluable patients to one of three treatment arms.

Efficacy stopping rules: This study will be monitored by Alliance Data and Safety Monitoring Board (DSMB) every 6 months for safely and efficacy. If at any time prior to full accrual the p-value for the Fisher's exact test that an arm is superior to the other arm given all available data falls below 0.001 then consideration will be given to stopping the trial early.

16.6 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either 1. the study re-opening to accrual or 2. at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe grade 4 or higher events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") that satisfy the following:

- If 3 or more patients in the first 20 treated patients (or 10% of all patients after 20 are accrued) experience a Grade 4 or higher non-hematologic adverse event and the adverse event rate is higher on either armodafinil arm than the placebo.

We note that we will review Grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.7 Study Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site [redacted]

The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. This study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

16.7.1 We will further carry out a single interim analysis when 30 patients per treatment arm are evaluable for the primary endpoint. We will use this interim analysis to verify that the 250 mg. dose arm is worthy of further accrual. If the conditional probability is less than 1% that the effect size is at least of moderate size given, the results (effect size) at that point, the 250 mg. dose arm will be considered for closing.

16.8 Missing Data

Routines developed by Mayo Clinic Cancer Center statisticians will be used to handle missing data in a number of ways including complete case analysis and imputation via nearest neighbor, mean value, last value, and zero value carried forward approaches. Multiple approaches are used so that the sensitivity of results to alteration in imputational assumptions may be assessed. The extent of missing data on the primary and secondary endpoints will be explored for non-random influences. Sensitivity analysis will be performed using various imputation techniques, to ensure

results are not unduly influenced by the presence of missing data. Other endpoints will be handled in a similar fashion (99).

16.9 Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

There is no information currently available regarding differential agent effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for such subset analyses. A total of 120 patients may be enrolled.

Based on prior studies involving similar disease sites, we expect about 6.7% of patients will be classified as minorities by race and about 50% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1	1	0	0	2
Asian	4	3	0	0	7
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	20	18	0		38
White	157	114	8	4	283
More Than One Race	0	0	0	0	0
Total	182	136	8	4	330

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 PATHOLOGY CONSIDERATIONS/TISSUE BIOSPECIMENS

None

18.0 RECORDS AND DATA COLLECTION PROCEDURES

Copies of forms and a data submission schedule are also available for download from the study page on the CTSU Web site.

18.1 Data collection and submission

Patient assessment questionnaires and neurocognitive testing booklets for A221101 are to be ordered prior to the registration of any patients. Samples of questionnaires/booklets are available in the protocol appendices for reference and IRB submission only. They are not to be used for patient completion. Patient assessment questionnaire/booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person or by mail.

See Section 4.0 for completion and submission of Neurocognitive Testing Booklets for all study sites.

The accompanying tables in Sections 18.2 detail the forms completion and submission time points.

18.1.1. Legacy NCCTG

All legacy NCCTG sites will submit electronic CRFs and enter QOL/Patient Assessment Booklet data via the NCCTG Remote Data Entry System.

18.1.2 Sites Not Previously Affiliated with NCCTG

For sites that were not previously affiliated with NCCTG, all paper CRFs and QOL/Patient Assessment Booklets will be forwarded to the following address:

18.2 Submission Timetable

Data Submission Schedule

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)		
	At baseline evaluation (≤2 weeks after registration)	**At end of week 4**	**At end of week 8**
On-Study Form	X		
Nurse/CRA Evaluation/Treatment Form		X	X
Baseline Adverse Event Form	X		
Adverse Event Form		X	X
Concomitant Steroid Medication Form	X	X	X
Patient Questionnaire Baseline Booklet	X		
Patient Questionnaire Booklet (Cycle 1)		X[1]	
Patient Questionnaire Booklet (Cycle 2)			X[1]
Patient Questionnaire Booklet Compliance Form		X[2]	X[2]
Neurocognitive Booklet	X	X[1]	X[1]
Neurocognitive Testing Booklet Compliance Form		X	X
End of Active Treatment/Cancel Notification Form			X
Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form	At each occurrence (see Section 10.0)		

1. Patient Questionnaire/Neurocognitive Testing Booklets **must** be used; copies are not acceptable for this submission.
2. This form must be completed **only** if the patient Questionnaire Booklet contains absolutely **NO** patient provided assessment information.

19.0 BUDGET

- Costs charged to patient: Routine clinical care
- Tests to be research funded: None
- Other budget concerns: Study agent/placebo will be provided to the patient free of charge.

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APPENDIX I: MODEL INFORMED CONSENT

A221101

A Phase III Randomized, Double-Blind Placebo Controlled Study of Armodafinil (Nuvigil®) To Reduce Cancer-Related Fatigue in Patients with High Grade Glioma

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

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

You are being asked to take part in this study because you are experiencing fatigue that is related to your cancer. Cancer related fatigue is a very common symptom in people with cancer.

Why is this study being done?

The purpose of this study is to:

- See if taking the study agent, armodafinil, at a dose of 150mg or 250mg, will improve problems with fatigue in patients who have been diagnosed with cancer and are experiencing fatigue.
- See the effects (good and bad) of taking Armodafinil compared to placebo (an inactive agent) on cancer related fatigue.

In this study, you will take either the study agent, armodafinil, or the placebo (inactive agent). You will not take both.

Armodafinil (Nuvigil®) is a medicine that is currently FDA approved to promote wakefulness in people who have sleep disorders. However, it is not been studied in people with cancer related fatigue.

How many people will take part in the study?

About 330 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study…

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

- Medical history (questions about your health and any medications you are taking), including weight and rating of how well you perform activities of daily living.
- General **neurological** examination
- Pregnancy test, if you have not already had one done and your doctor thinks this is needed (if you are a female and able to become pregnant)

During the study…

You will have already had radiation therapy or surgery for your cancer.

Before you start taking the study agent, armodafinil or placebo, you will complete a booklet of questionnaires. This booklet contains 6 brief questionnaires about the fatigue related symptoms you may be experiencing, and should take a total of 20-25 minutes to complete.

You will also be asked to complete a cognitive test (memory and concentration skills test). This will be done three times; once before you start taking the study agent, once at 4 weeks and once again at the end of the 8 week period, when you are finished taking the study agent. This is to see how the study agent is affecting your memory and concentration. For the test, you will be asked some questions about your memory and concentration by someone with specialized training in this area. This testing will be done at your doctor's office, and will take about 20-30 minutes to complete.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have a one in three chance of being placed in any group.

> **If you are in group 1**, you will take a dose of the armodafinil (150 mg) by mouth, every day in the morning. You will take this every day for 8 weeks.
>
> **If you are in group 2**, you will take a dose of the placebo pill (inactive ingredient) by mouth, every day in the morning. You will take this every day for 8 weeks.
>
> **If you are in group 3**, you will take a dose of the armodafinil (250 mg) by mouth, every day in the morning. You will take this every day for 8 weeks.

If you miss taking a tablet in the morning, you can take the tablet that day as long as you take it at least 12 hours before the next dose.

You will also complete a booklet of questionnaires at the end of weeks 4 and 8. This booklet contains the same 6 brief questionnaires about the fatigue, memory, and concentration that you completed before you started taking the study agent/placebo. This should take a total of 20-25 minutes to complete (as described above).

Someone from the study team will call you at the end of week 4 and week 8 and to see how you are doing and answer questions.

When I am finished taking the study agent/placebo…

You will complete the booklet of questionnaires (end of week 8) regarding your fatigue related symptoms, and undergo cognitive (memory and concentration skills) testing (as described above).

How long will I be in the study?

You will be asked to take the study agent or placebo for 8 weeks.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study agent, armodafinil, can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

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

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study agent. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the study agent, armodafinil, include those which are:

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving armodafinil, from 4 to 20 may have:
• Headache • Trouble sleeping • Nausea • Dizziness • Anxiety • Diarrhea

RARE In 100 people receiving armodafinil, 3 or fewer may have:
• Upper abdominal pain • Fatigue • Rash • Agitation, attention disturbance, or nervousness • Decreased appetite, anorexia • Constipation • Shortness of breath • Excessive sweating • Flu-like symptoms • Pain • Numbness and tingling • Frequent urination • Fever • Thirst • Tremor or shakiness • Dry mouth • Vomiting • High blood pressure

RARE, AND SERIOUS In 100 people receiving armodafinil, 3 or fewer may have:
• Severe headaches • Severe allergic reaction • Increased heart rate • Irregular heart beat • Depression • Increased risk of suicidal thoughts • Stevens-Johnson Syndrome (see below)

Stevens-Johnson syndrome is a rare, serious disorder in which your skin and mucous membranes react severely to a medication or infection. Often, Stevens-Johnson syndrome begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters, eventually causing the top layer of your skin to die and shed. Stevens-Johnson syndrome is an emergency medical condition that usually requires hospitalization. Recovery after Stevens-Johnson syndrome can take weeks to months, depending on the severity of your condition. If you develop Stevens-Johnson syndrome and your doctor determines that it might have been caused by the study medication, you'll need to discontinue it.

Armodafinil has not been shown to produce impaired judgment, thinking or affect motor skills, but due to the action of the medication, you should use caution when operating automobile or other hazardous machinery.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope armodafinil will be helpful against cancer related fatigue, there is no proof of this yet. We do know that the information from this study will help doctors learn more about treatment for cancer related fatigue. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer related fatigue without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Alliance Researchers

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a service sponsored by the NCI to provide greater access to cancer trials

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

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

You will not need to pay for tests and procedures which are done just for this research study. This test is:

- Cognitive test

The study agents, armodafinil and placebo, will be supplied at no cost to you.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the armodafinil for some reason. If this would occur, other possible options are:

- You might be able to get the armodafinil from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no armodafinil available at all, no one will be able to get more and the study would close.
- If a problem with getting armodafinil occurs, your study doctor will talk to you about these options.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage .You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ [*investigator's name(s)*], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [*telephone number*].

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

What are my rights if I take part in this study?

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

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

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

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

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

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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

Signature

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

Participant _____

Date _____

APPENDIX II: PATIENT INFORMATION SHEETS

Baseline Patient Information Sheet

You have been given a booklet to complete for this study. The booklet contains some questions about your quality of life and health status as a patient receiving treatment. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. The booklet contains six sets of questions:

    a. Brief Fatigue Inventory
    b. PROMIS Fatigue Short Form
    c. PRO-CTCAE
    d. Linear Analogue Self-Assessment Scale
    e. FACT-Cog
    f. Godin Leisure – Time Exercise Questionnaire

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please return the booklet when you are finished

Thank you for taking the time to help us.

Patient Information Sheet
(First 4 weeks)

You have been given a booklet to complete for this study. The booklet contains some questions about your quality of life and health status as a patient receiving treatment. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. The booklet contains six sets of questions to be completed at the end of week 4:

    a. Brief Fatigue Inventory
    b. PROMIS Fatigue Short Form
    c. PRO-CTCAE
    d. Linear Analogue Self-Assessment Scale
    e. FACT-Cog
    f. Godin Leisure – Time Exercise Questionnaire

2. Directions on how to complete each set of questions are written on the top of each set.

3. A study nurse will call you on week 4 to answer any questions you might have. You will be given the nurse's name and telephone number. You can call anytime with any concerns or questions.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. At the end of week 4, please return the booklet when you are finished

Thank you for taking the time to help us.

Patient Information Sheet
(End of Week 8)

You have been given a booklet to complete for this study. The booklet contains some questions about your quality of life and health status as a patient receiving treatment. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. The booklet contains six sets of questions to be completed at the end of week 8:

    a. Brief Fatigue Inventory
    b. PROMIS Fatigue Short Form
    c. PRO-CTCAE
    d. Linear Analogue Self-Assessment Scale
    e. FACT-Cog
    f. Godin Leisure – Time Exercise Questionnaire

2. Directions on how to complete each set of questions are written on the top of each set.

3. A study nurse will call you week 8 to answer any questions you might have. You will be given the nurse's name and telephone number. You can call anytime with any concerns or questions.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. At the end of week 8, Please return the booklet when you are finished

Thank you for taking the time to help us.

APPENDIX III: BRIEF FATIGUE INVENTORY

BRIEF FATIGUE INVENTORY

Throughout our lives, most of us have times when we feel very tired or fatigued.

Have you felt unusually tired or fatigued in the last week? ***(check one)***
Yes_____ **No** _____

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW?

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No fatigue										As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. *General Activity*

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. *Mood*

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. *Walking Ability*

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. *Normal work (includes both work outside the home and daily chores)*

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. *Relations with other people*

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. *Enjoyment of life*

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

APPENDIX IV: PROMIS FATIGUE SHORT FORM

PROMIS Item Bank v. 1.0 - Fatigue -Short Form 7a

Fatigue - Short Form 7a

Please respond to each question by marking one box per row.

In the past 7 days...

		Never	Rarely	Sometimes	Often	Always
FATEXP20	How often did you feel tired?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP5	How often did you experience extreme exhaustion?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP18	How often did you run out of energy?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP33	How often did your fatigue limit you at work (include work at home)?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP30	How often were you too tired to think clearly?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP21	How often were you too tired to take a bath or shower?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40	How often did you have enough energy to exercise strenuously?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

APPENDIX V: LINEAR ANALOGUE SELF ASSESSMENT (LASA)

LINEAR ANALOGUE SELF ASSESSMENT

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

How would you describe:

1. your overall Quality of Life?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

2. your overall mental (intellectual) well being?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

3. your overall physical well being?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

4. your overall emotional well being?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

5. your level of social activity?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

6. your overall spiritual well being?

1	2	3	4	5	6	7	8	9	10
As bad as It can be									As good as It can be

7. the frequency of your pain?

1	2	3	4	5	6	7	8	9	10
No Pain									Constant Pain

8. the severity of your pain, on the average?

1	2	3	4	5	6	7	8	9	10
No Pain									Pain as bad as you can imagine

9. your level of fatigue, on the average?

1	2	3	4	5	6	7	8	9	10
No fatigue									Constant tiredness

10. your level of support from friends and family?

1	2	3	4	5	6	7	8	9	10
No support									Highest level of support

11. your financial concerns?

1	2	3	4	5	6	7	8	9	10
Constant concerns									No concern

12. your legal concerns (will, advanced directives, etc.)?

1	2	3	4	5	6	7	8	9	10
Constant concern									No concern

APPENDIX VI: FACT-COG

FACT-Cog (Version 3)

Below is a list of statements that other people with your condition have said are important. **By circling one (1) number per line, please indicate how often each of the following has occurred during the past 7 days.**

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogA1	I have had trouble forming thoughts 0	0	1	2	3	4
CogA3	My thinking has been slow 0	0	1	2	3	4
CogC7	I have had trouble concentrating 0	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet 0	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object 0	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others 0	0	1	2	3	4

CogF19	I have walked into a room and forgotten what I meant to get or do there 0	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake 0	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced 0	0	1	2	3	4

Below is a list of statements that other people with your condition have said are important. **By circling one (1) number per line, please indicate how often each of the following has occurred <u>during the past 7 days.</u>**

		Never	**About once a week**	**Two to three times a week**	**Nearly every day**	**Several times a day**
CogF25	My reactions in everyday situations have been slow 0	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual 0	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
CogMT2	I have difficulty shifting back and forth between different activities that require thinking	0	1	2	3	4

Please answer the questions below with regard to all the above concerns that you have identified. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much
CogQ35	I have been upset about these problems 0	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work 0	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy 0	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4

Below is a list of statements that other people with your illness have said are important**. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

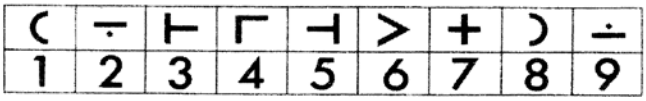
		Not at all	A little bit	Some-what	Quite a bit	Very much
Cog PC1	I have been able to concentrate	0	1	2	3	4
Cog PV1	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PM1	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PF1	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PCH 1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PCH 2	My memory is as good as it has always been	0	1	2	3	4
Cog PMT 1	I am able to shift back and forth between two activities that require thinking					
Cog PMT 2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

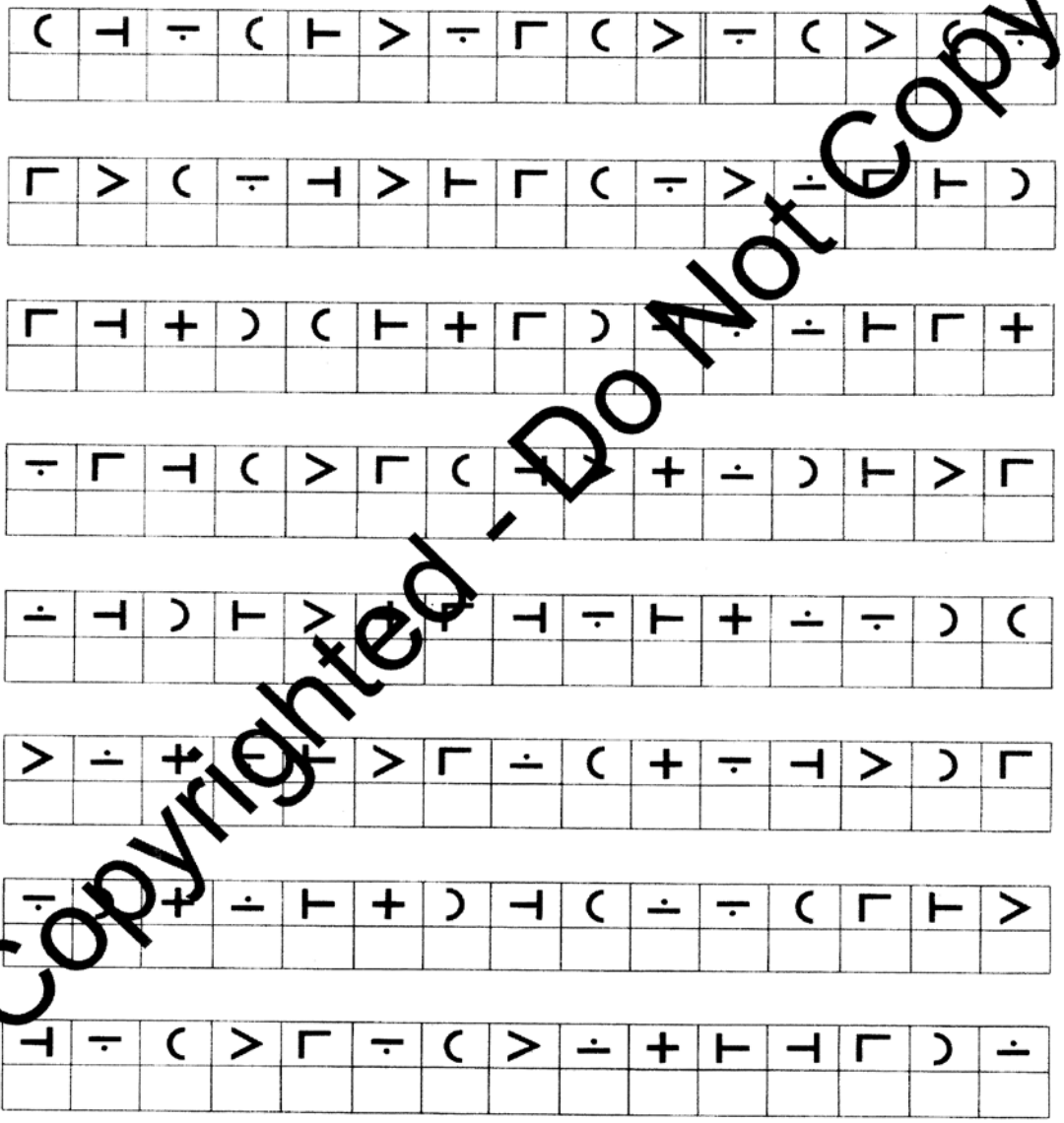
APPENDIX VII: COGNITIVE TESTING

Neurocognitive Testing

Symbol Digit Modalities Test - copyright©

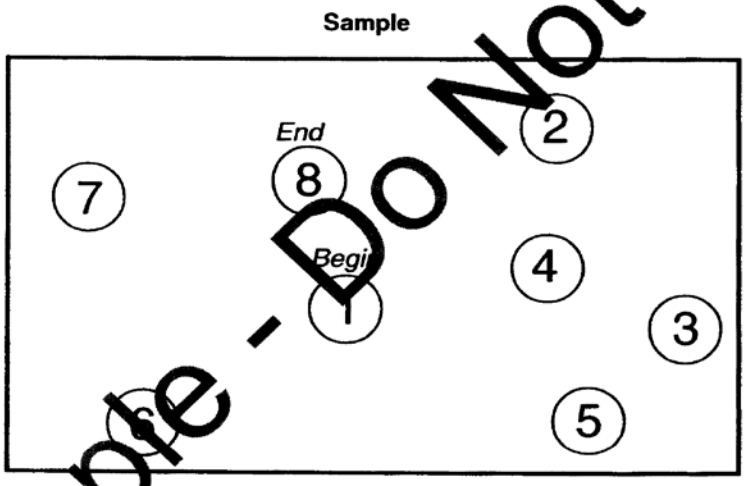
KEY

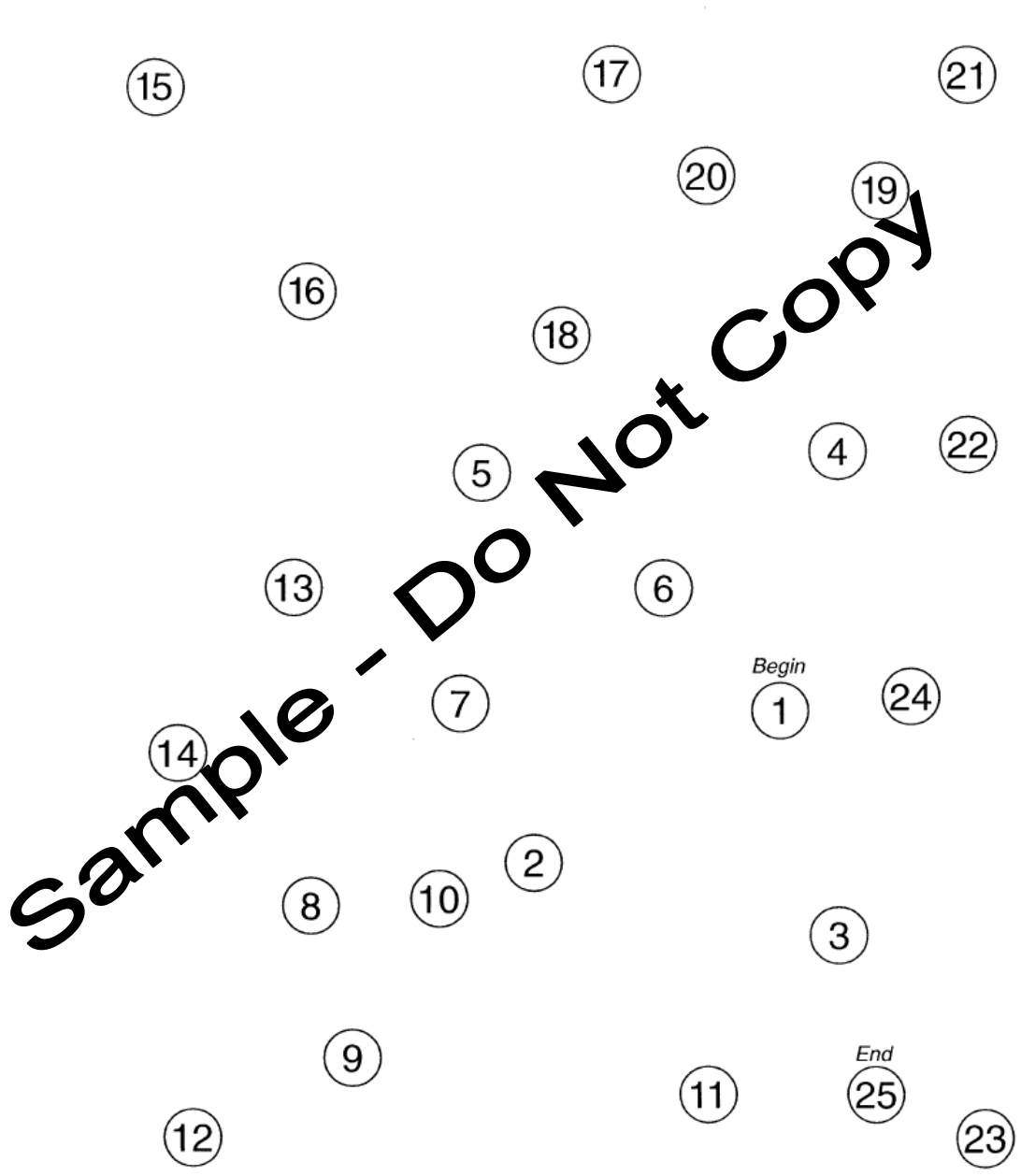




Trail Making

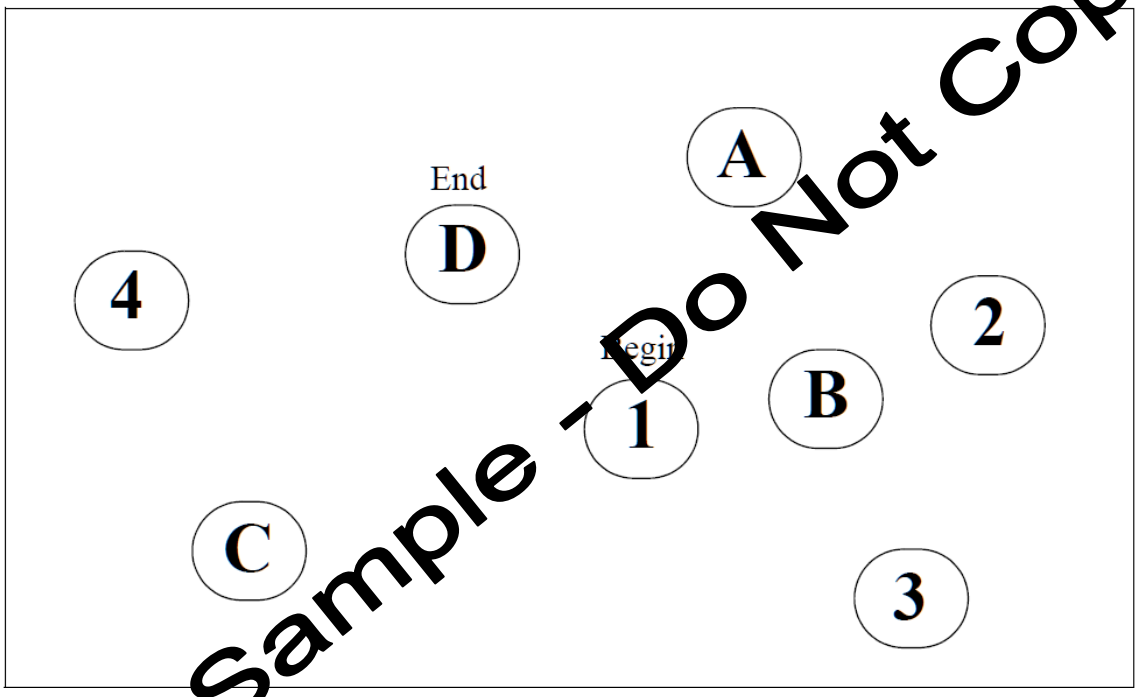
Part A

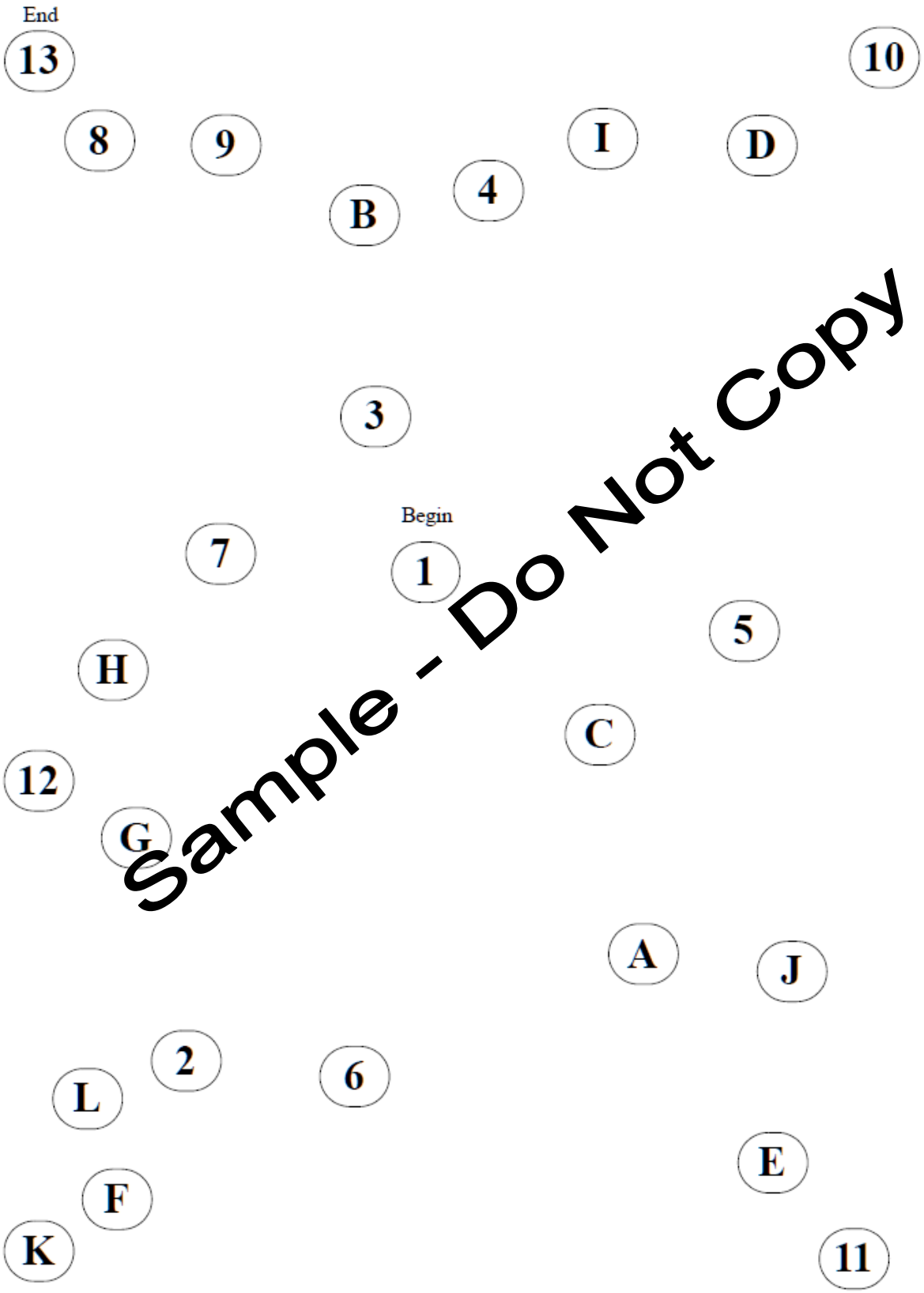




FOR PRACTICE USE ONLY

TRAIL MAKING
PART B
SAMPLE





APPENDIX VIII: ADMINISTRATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY

ADMINISTRATION PROCEDURES FOR THE NEUROCOGNITIVE TEST BATTERY

Please note: All personnel who administer the cognitive testing will need to be certified. Please see section 4.1

1. **Testing should be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.**

   PLEASE NOTE: If a patient is unable to complete the test due to cognitive deterioration, it is best to attempt the test and proceed until the patient meets discontinuation criteria. Then mark down at the bottom of each test form "Discontinued" and fill in the reason (e.g. could not understand the instructions). This is much preferred to not completing the test at all and should not be frustrating to the patient as it will only take a few minutes of the patient's time.

2. **Originals of the test booklets should be mailed to**
   [redacted]

3. **Please keep copies of all original test booklets. In the event of questions, contact the RPS III or QAS of the study (contact information can be found in the protocol on the Resource page.**

4. **Patients should not be given copies of their tests to avoid learning the material between test administrations.**

Setting up for Neuropsychological Testing

Set up of testing situation:

- ☐ **Private room**
- ☐ **Door that closes**
- ☐ **Quiet**
- ☐ **Alone with just the patient-- No family members**
- ☐ **May want to hang a sign that says "do not disturb"**
- ☐ **Some tests are timed – it is very important not to be interrupted**
- ☐ **Desk for you both to write on (clipboard works in a pinch)**
- ☐ **Stopwatch**
- ☐ **Black ink pens (one for you and one for the patient)**

Testing tips

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

TEST INSTRUCTIONS
Administer the tests in the following order to every patient at every visit

1. Symbol Digit Modalities Test (Smith, 1982)

The SDMT requires the subject to insert a numbers matching to geometric figures presented in random order. The appropriate number is shown in a key containing the Arabic numerals 1 through 9, each of which is paired with a different geometric symbol. To administer the test, place the form in front of the examinee. Read the instructions verbatim. These are taken directly from the test manual (Smith, 1982) and read as follows:

"Please look at these boxes at the top of the page. You can see that each box in the upper row has a little mark in it. Now look at the boxes in the row just underneath the marks. Each of the boxes under the marks has a number. Each of the marks in the top row is different, and under each mark in the bottom row is a different number.

Now look at the next line of boxes (examiner points to the line of boxes) just under the top two rows. Notice that the boxes on the top have marks, but the boxes underneath are empty. You are to fill each empty box with the number that should go there according to the way they are paired in the key at the top of the page. For example, if you look at the first mark, and then look up at the key, you will see that the number 1 goes in the first empty box. So write the number 1 in the first box. Now, what number should you put in the second box? (Number 5) That's right. So write the number 5 in the second box. What number goes in the third box? (Number 2) Two, right. That is the idea. You are to fill in each of the empty boxes with the numbers that should go in them according to the key. Now for practice, fill in the rest of the boxes until you come to the double line. When you come to the double line, stop."

The examiner should check to see that each examinee understand the task. Any errors made in the first 10 practice responses (before the double line) should be immediately pointed out by the examiner and corrected by the examinee. If an examinee has not understood the nature of the task, the instructions are repeated with further examples until the nature of the test is clearly understood. The examinee then continues with the following instructions.

"You will have a minute for each letter. The first letter is '___' (see scoring sheet).

****Allow exactly one minute for each letter****

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

Recording and Scoring:

- **The COWA provides lines on which the patient's responses can be entered (e.g.,write in the word that is said by the patient). If his/her speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response.**
- **Incorrect responses either should not be recorded or, if recorded, should be struck through with a line.**
- **If the patient provides more responses than there are lines on the record sheet, place check marks in the boxes to indicate correct responses only.**
- **Count all the correct responses. The number of correct words should be indicated below each column.**

Comments on scoring:

- **Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.**
- **The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word (e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs) are not considered correct responses.**
- **Patients often give both a verb and a word derived from the verb or adjective (e.g., fun-funny; sad-sadness). These are not considered correct responses. On the other hand, if the word refers to a specific object (e.g., foot-footstool; hang-hanger), it would be counted as a correct answer.**
- **Many words have two or more meanings (e.g., foot; can; catch; hand). A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.**
- **Slang terms are OK if they are in general use.**
- **Foreign words (for example, pasta; passé; lasagna) can be counted as correct if they can be considered part of the lexicon of the relevant language, the criterion being their listing in a standard dictionary of that language. All incorrect and repeated responses MUST be crossed out with one single line, initialed and dated. Additionally, all duplicate entries that have been verified to have different meanings must be marked "ok", initialed and dated. Refer to the descriptions above for guidelines for acceptability. Add the total number of correct responses in each column and input the totals where indicated on the COWA worksheet.**
- **If the test is discontinued or omitted, please mark this on the bottom of the test form.**

3. TRAIL MAKING TEST [Timed Test]

Instructions are included verbatim in the test booklet

Part A – Sample:

The Sample for Part A must be completed/attempted by each patient at every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table). Give the patient a black pen and say:

Examiner: "On this page (point) are some numbers. Begin at number 1 (point to 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4), and so on, in order, until you reach the end (point to the circle marked END). Draw the lines as fast as you can. Ready, begin."

If the patient completes Sample A correctly and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it.

The following explanations of mistakes serve as illustrations:

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

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
Examiner: "Remember, begin at number 1 (point to 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4) and so on, in order, until you reach the circle marked END (point). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making A & B Scoring (TMABS) sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part A – Test:

After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:
Examiner: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (point) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4) and so on, in order, until you reach the circle marked END (point). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."

- **Start timing as soon as the instruction is given to "begin."**
- **Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred (In other words, have them go back to the *last correct circle*).**
- **The patient must complete the test in 3 minutes or less**
- **DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END."**
- **If the patient does not complete the test within 3 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Complete the Trail Making A & B Scoring (TMABS) sheet indicating the reason the test was terminated** and the last correct number reached on the test.
- **If the patient successfully completes the test, record the time to completion on the Trail Making A & B Scoring (TMABS) sheet in minutes and seconds. Then say, "That's fine. Now we'll try another one."**

Part B – Sample:

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

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it.

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

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:
Examiner: "Now you try it. Remember, begin at number 1 (point to 1) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3) and so on, in order, until you reach the circle marked END (point). Ready, begin."

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making A & B Scoring (TMABS) sheet. If the patient completes Sample B correctly and appears to understand what to do, proceed immediately to Part B.

Part B – Test:

After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

Examiner: " Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (point) and draw a line from 1 to A (point to A), A to 2 (point to 2), 2 to B (point to B), B to 3 (point to 3), 3 to C (point to C) and so on, in order, until you reach the circle marked END (point). Remember, first you have a number (point to 1), then a letter (point to A), then a number (point to 2), then a letter (point to B), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."

- **Start timing as soon as the instruction is given to "begin."**
- **Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred (In other words, have them go back to the *last correct circle*).**
- **The patient must complete the test in 5 minutes or less.**
- **DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END."**
- **Record the time to completion on the Trail Making A & B Scoring (TMABS) in minutes and seconds.**
- **If the patient does not complete the test within 5 minutes terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Complete the Trail Making A & B Scoring (TMABS) sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.**
- **If the patient successfully completes the test, record the time to completion on the Trail Making A & B Scoring (TMABS) sheet in minutes and seconds.**

APPENDIX IX: NEUROCOGNITIVE EVALUATIONS SUBMISSION FAX FORM

Neurocognitive Evaluations Submission Fax Form

Fax completed form to:

[redacted]

From: _____

Date: _____

Re: Neurocognitive Evaluations Booklet Submission

Attention: A completed Neurocognitive Evaluations booklets (completed Patient and Examiner Questionnaire Booklets) have been sent to you via surface mail, as of _____(date).

Contact Information: _____

Person administering test: _____

Name of site: _____

Phone: _____

Email: _____

Patient's study ID #: _____

APPENDIX X: BAYES SHADOW STATISTICAL DESIGN

Bayes Shadow Statistical Design

The primary endpoint for the trial is the response rate in terms of a clinically meaningful improvement in patient-reported fatigue, defined as at least a two-point improvement in fatigue as measured by the worst fatigue item from the Brief Fatigue Inventory at 8 weeks, and the design proposed for this study will randomize a minimum of 30 evaluable patients and a maximum of 120 evaluable patients to one of three treatment arms The Bayesian adaptive randomization design (98) will work as follows The first 30 patients will be randomized in a 1:1:1 fashion to the three treatment arms (block size of 30 will be used to guarantee an equal number of patients are randomized to each treatment arm). After the 30th patient has been randomized, the adaptive randomization procedure will begin. As a shadow design, we will use the data from the completed Fisherian design and then assess the different assignations that would have been made via the Bayes design and its impact on the trial results.

Adaptive randomization: We assume that the fatigue response outcome, denoted $X_{i,j}$, of patient i on treatment j derives from a Binomial(π_j) distribution (j=1 for placebo; j=2 for armodafinil 150 mg). We assume that π_j derives from a Beta (α_j, β_j) distribution. Given limited historical data, we use a uniform non-informative prior for each arm (α_1=α_2=1; β_1=β_2=1). We repeat this calculation for the comparison of the placebo versus the armodafinil 250 mg arm and normalize the result to get three probabilities for treatment assignation.

As each patient is enrolled, the randomization probability for each treatment arm is recomputed using all currently available fatigue response data from already accrued patients. The randomization procedure computes the posterior probability for each treatment of being the best between the two treatments (where p_j = probability that treatment j is better than the other treatment) and assigns the patient to arm j with probability p_j (i.e., λ=1 in the notation of Cook [100]). This procedure uses all observed fatigue response data at the time of the patient's randomization to unbalance the randomization probabilities in favor of the treatment arm having comparatively superior symptom response outcomes.

Efficacy stopping rules: If at any time prior to full accrual the probability that an arm is superior to the other arm given all available data falls below 0.05 (P_L in the notation of the Adaptive Randomization software used below), that arm is suspended (though it potentially could reopen should the results on the other arm substantially worsen). If at any time prior to full accrual the probability that an arm is superior to the other arm given all available data rises above 0.95 (P_U in the notation of the Adaptive Randomization software used below), that arm is declared the winner and the trial is stopped early.

Decision rule: If the trial runs through completion without early stopping and if the largest probability for the two armodafinil treatment arms is better than that for the placebo arm is greater than 0.80 (P_U* in the notation of the Adaptive Randomization software used below), then that treatment is declared the winner of the trial.

Operating characteristics: Operating characteristics of a clinical trial with the above parameters and accrual rate were simulated (10,000 replicates) using software developed by the M. D. Anderson Cancer Center Department of Biostatistics (available at:http://biostatistics.mdanderson.org/SoftwareDownload/):

Arm[1]	True Confirmed Fatigue Response Rate	Pr(Selected)[2]	Pr(Selected Early)[3]	Pr(Stopped Early)[4]	Average Number of Evaluable Patients Treated	Average Trial Duration
1	10%	0.20	0.07	0.07	34	27.6 mo
2	10%	0.20	0.07	0.07	34	
1	10%	0.09	0.04	0.21	29	26 mo
2	15%	0.41	0.19	0.04	36	
1	10%	0.03	0.02	0.39	24	23.5 mo
2	20%	0.63	0.36	0.02	35	
1	10%	0.02	0.01	0.57	20	20.4 mo
2	25%	0.80	0.54	0.01	33	
1	10%	<0.01	<0.01	0.73	18	17.4 mo
2	30%	0.90	0.69	<0.01	29	

1. 1=placebo, 2=best of armodafinil arms.
2. The overall probability that the given arm is selected as being the best treatment after the trial has ended.
3. The probability that the given arm is selected as being the best treatment arm early (prior to all patients being enrolled).
4. The probability that the given arm is dropped for any reason (due to futility or another arm being selected).

Site Ordering Instructions and Order Forms: Armodafinil and Placebo

Background: The NCCTG/Alliance research base pharmacy will deviate from their standard operational policy of supplying study agent to the main NCCTG, CALGB and ACOSOG memberships. For this trial, the research base pharmacy will send one patient specific supply (one bottle) directly to each participating main membership or each participating affiliate site upon receipt of an order from the participating site. This order must be completed each time a study participant is enrolled.

Starter Supplies: Each treating location, must request one patient-specific bottle each time a patient is registered in the trial by completing the Alliance Clinical Order/Return Form located on page 2 of this appendix. Note a sample form is included (page 3 of this appendix)

Please be certain to include a ***complete shipping address*** for the treatment site.

Please include your ***patient's registration number and initials on the form***. Please also include the DEA Registration Number of your Pharmacy or investigator on the order form.

The site must also complete the Alliance clinical drug order/return form located on page 2 of this appendix, and fax it to the number listed on the form.

Note: ***Allow three business days for the delivery of the order***.
The shipment of Armodafinil/placebo will be provided in bottles, with each bottle containing 56 tablets.

A221101 CLINICAL DRUG ORDER FORM
Alliance

FAX orders to: [redacted]
Cancer Treatment Pharmacy Svc.

MAIL orders/returns to:

[redacted]

The drugs listed below are requested for the use of (please type or print):

Dr. _____

Designee/Requester (if other than investigator) (please type or print):

Name: _____ Title: _____

Telephone Number: _____ Fax Number: _____

Gonda 10 USE ONLY

_____
filled by

_____
checked by

_____
date

_____
Investigator/Designee Signature

Date *(dd/Mon/yyyy):* _____

Site DEA Registration Number: _____
(*Example: FM1234567)*

Protocol Number	Patient Study ID Number	Patient Initials	Drug Name	Strength & Dosage Form (vials, tablets, etc.)	Quantity Ordered (vials, bottles, etc.)	Date Needed	------	**Bottle #**
A221101	**2XXXXXX**	**Example ABC**	**Armodafinil 150mg or armodafinil 250mg or placebo tablets**	**56 tablets per bottle**	**One bottle**	**XX/XX/XXXX**		

SHIPPING ADDRESS:

NOTE: Urgent Shipments must be accompanied by an express courier account number.

Express Courier Name:

Express Courier Acct No.: __ __ __ __ - __ __ __ __ - __

INSTRUCTIONS:
1. One item or protocol per line
2. When **requesting** drugs: Fill in all sections completely, **except** shaded areas.
3. Must include official shipping address, site DEA registration number, patient initials, and patient study ID.
4. Sign and date the order/return.

A221101 CLINICAL DRUG ORDER/RETURN FORM
Alliance

FAX orders to: [redacted]
Cancer Treatment Pharmacy Svc.

MAIL orders/returns to:

[redacted]

The drugs listed below are requested for the use of (please type or print):

Dr. **Investigator Name**

Designee/Requester (if other than investigator) (please type or print):

Name: **Ordering Designee** Title: **As needed**

Telephone Number: **Complete number** Fax Number: **Complete number**

Gonda 10 USE ONLY

filled by

checked by

date

Investigator/Designee Signature

Date

COMMENTS:
Site DEA Registration Number:

Protocol Number	Patient Study ID Number	Patient Initials	Drug Name	Strength & Dosage Form (vials, tablets, etc.)	Quantity Ordered (vials, bottles, etc.)	Date Needed	------	**Bottle#**
A221101	**2XXXXXX**	**Example: ABC**	**armodafinil 150mg or armodafinil 250mg or placebo tablets**	**56 tablets per bottle**	**One bottle**	**XX/XX/XXXX**		

SHIPPING ADDRESS:
Site Name:
Facility:
Department:
Street Address:
City, State:
Zip:

NOTE: Urgent Shipments must be accompanied by an express courier account number.

Express Courier Name:

Express Courier Acct No.: __ __ __ __ - __ __ __ __ - __

INSTRUCTIONS:
1. One item or protocol per line
2. When **requesting** drugs: Fill in all sections completely, **except** shaded areas.
3. When **returning** drugs: Fill in all sections completely, **including** shaded areas.
4. Must include official shipping address.
5. Sign and date the order/return.

APPENDIX XII: NURSE/CRA PHONE CONTACT

Nurse/CRA Phone Contact Guide

Patient Phone No. _____
Best Dates/Times to call_____

FOLLOW UP:

Phone call schedule: Call patient at home the end of study weeks 4 and 8. This is to remind patient to take the study agent as instructed, document compliance, encourage completion of the booklet, and address problems. If the patient is seen in clinic, this phone call can be omitted.

•

3. Items to document:
   - ☐ Date of phone call
   - ☐ Study week
   - ☐ Questions/Comments
   - ☐ Performance Status Score
   - ☐ AE assessment end of weeks 4 and 8

   If the patient reports any side effects, please document:
   - o Side effects:
     - ☐ Headache
     - ☐ Any others - Severity and attribution, if applicable.

4. Reinforce compliance with study medication.

5. Reinforce completion of questionnaires and request return of them at end of the month.

APPENDIX XIII: GODIN LEISURE TIME EXERCISE QUESTIONNAIRE (GLTEQ)

Patient ID

MDS Study

Patient Initials

Godin Leisure - Time Exercise Questionnaire

○ Baseline ○ Post Treatment

1. Considering the **previous 7-Day period (this past week)**, how many times did you do the following kinds of exercise for **more than 15 minutes** during your **free time**.

a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY) (i.e. running, jogging, hockey, football, soccer, squah, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling, spinning)

b) MODERATE EXERCISE (NOT EXHAUSTING) (i.e. fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing, yoga, tai chi, pilates)

c) MILD EXERCISE (MINIMAL EFFORT) (i.e. archery, fishing from river bend, bowling, horseshoes, golf, snow-mobiling, easy walking)

2. Considering the **previous 7-Day period (this past week)**, during your leisure-time, how often did you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?

often sometimes never/rarely

APPENDIX XIV: PRO-CTCAE

PRO-CTCAE Questionnaire

PRO-CTCAE items for fatigue and cognitive function

1. In the last 7 days, what was the SEVERITY of your fatigue, tiredness, or lack of energy at its WORST:

   None / Mild / Moderate / Severe / Very severe

2. In the last 7 days, how much did fatigue, tiredness, or lack of energy INTERFERE with your usual or daily activities:

   Not at all / A little bit / Somewhat / Quite a bit / Very much

3. In the last 7 days, what was the SEVERITY of your problems with concentration at their WORST:

   None / Mild / Moderate / Severe / Very severe

4. In the last 7 days, how much did problems with concentration INTERFERE with your usual or daily activities:

   Not at all / A little bit / Somewhat / Quite a bit / Very much

5. In the last 7 days, what was the SEVERITY of your problems with memory at their WORST:

   None / Mild / Moderate / Severe / Very severe

6. In the last 7 days, how much did problems with memory INTERFERE with your usual or daily activities:

   Not at all / A little bit / Somewhat / Quite a bit / Very much

ECOG PERFORMANCE STATUS

Grade	
0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	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 (Karnofsky 70-80).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 percent of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50 percent or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

APPENDIX XVI: COPY OF FDA IND EXEMPTION LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116927

EXEMPT IND

Alyx B. Porter, M.D.
5777 East Mayo Boulevard
Phoenix, Arizona 85054

Dear Dr. Porter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Nuvigil® (armodafinil).

After reviewing the information contained in your submission, we have concluded that your study, protocol N10C3, entitled "A Phase III Randomized, Double-Blind Placebo Controlled Study of Armodafinil (Nuvigil®) To Reduce Cancer-Related Fatigue in Patients with Gioblastoma Multiforme", meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.

The IND regulations [21 CFR 312.2(b)] state that the clinical investigation of a drug product, including a biological product, that is lawfully marketed in the United States, is exempt from the requirements for an IND if all of the following apply:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.

2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.

3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.

4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50).

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

Reference ID: 3216245|

In addition, 21 CFR 312.2(b)(5) exempts from the IND requirements a clinical investigation that involves use of a placebo if the investigation does not otherwise require submission of an IND. We remind you that exemption from the requirements for an IND does not in any way exempt you from complying with the requirements for informed consent under 21 CFR 50.20 or from initial and continuing Institutional Review Board review under 21 CFR Part 56. You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 U.S.C. §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Please note that, if in the future you submit an application under sections 505, 515, or 520(m) of the FDCA (21 USC §§ 355, 360(e), or 360(j)(m)), or under section 351 of the PHS Act (21 U.S.C. § 262), or you submit a report under section 510(k) of the FDCA (21 USC § 360(k)), the application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act (42 USC § 282(j)) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) control numbers (42 USC § 282(j)(5)(B)). Additional information regarding the certification is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trial(s) is available at the Protocol Registration System website (http://prsinfo.clinicaltrials.gov/).

For additional information about IND regulations, you can check our web site at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm

If you have any questions, call Elleni Alebachew, Regulatory Project Manager, at (301) 796 5225.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALICE KACUBA
11/13/2012
Signing for Dr. Justice.

Reference ID: 3216245