The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

A randomized placebo-controlled trial of Cognitive Behavioral Therapy for Insomnia (CBT-I) and Armodafinil for Insomnia following Cancer Treatments

Roscoe, et al

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UNIVERSITY OF ROCHESTER CANCER CENTER

Cognitive Behavioral Therapy +/- Armodafinil for Insomnia and Fatigue following Chemotherapy (UCCS07090)

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Modified 9/5/2008
Modified 12/01/2008
Modified 7/23/2009
Modified 9/2/2009

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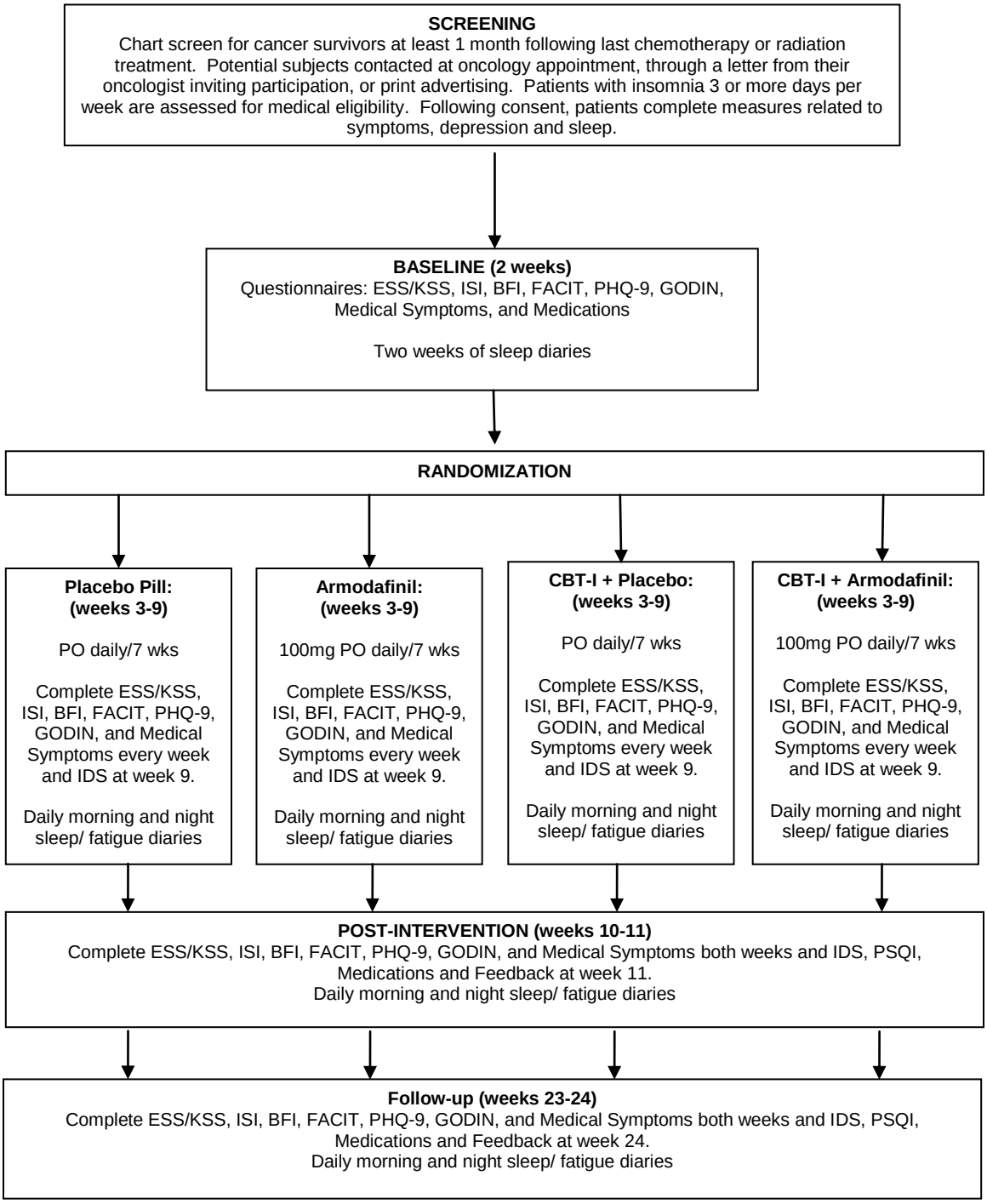

1.0 Background

Insomnia in Cancer Patients: Insomnia has been reported in several studies of patients receiving chemotherapy,[1-5] and at a rate that appears to be nearly three times as prevalent as in the general population.[6,7] Interestingly, data suggest that insomnia may persist well beyond the active illness and/or on-going treatment.[8-10] The occurrence of insomnia is sufficiently frequent, and experienced by cancer patients as sufficiently severe enough as to warrant medical intervention — so much so that between a quarter and a half of all prescriptions written for cancer patients are for hypnotics.[11,12]

Characterization of Cancer-Related Fatigue (CRF): Cancer chemotherapy frequently results in patient distress, the most common aspect of which is fatigue.[13-15] Patients report that CRF is more distressing and has a greater impact on their daily activities and QOL than other cancer-related symptoms such as pain, depression, and nausea.[16] Frequently, patients report that fatigue begins with treatment, continues during the course of chemotherapy, and declines somewhat but persists at a higher-than-baseline rate after treatment is over, sometimes lasting for months, or even years, after the end of cancer treatment.[3,17-23]

Connection between CRF and Sleep Problems: There is now a body of literature that supports the concept that CRF does not occur in isolation but instead occurs in association with sleep disturbance. While most of these studies are correlational in nature, it is generally the case that insomnia is: 1) positively correlated with fatigue, 2) is more severe in fatigued vs. non-fatigued patients, and 3) a significant predictor of fatigue.[(e.g.,4,3,24,25)] These data are consistent with the concept that fatigue and insomnia are reciprocally related and allow for the possibility that treatment for one may impact the other.

Efficacy of CBT-I for Insomnia in Breast Cancer Survivors: Although a great deal of evidence indicates that CBT-I is effective for the treatment of insomnia in the general population, evidence regarding its effectiveness in treating sleep problems in breast cancer patients post-treatment is limited. Providing additional data on the efficacy of CBT-I in cancer survivors is, in fact, one of the primary reasons for the proposed research.

Efficacy and Safety of Modafinil in Reducing Daytime Sleepiness and Fatigue: Modafinil (Provigil®) is marketed in the United States (US) for the management of excessive daytime sleepiness (EDS). The US Drug Enforcement Agency (DEA) lists modafinil as a scheduled medication, but classifies it as a level IV controlled substance. The wakefulness-promoting efficacy of modafinil was originally demonstrated in two nine-week, Phase 3, double-blind, placebo-controlled trials that enrolled a total of 558 narcolepsy patients with excessive daytime sleepiness.[26,27] The longer-term efficacy and safety of modafinil has also been assessed for up to 136 weeks of open-label treatment following these two nine-week, double-blind studies.[28,29] In addition to the treatment of excessive sleepiness associated with narcolepsy, modafinil reduces excessive sleepiness associated with obstructive sleep apnea, shift-work sleep disorder, myotonic dystrophy, and Parkinson's disease. Modafinil has also been shown to reduce fatigue in patients with narcolepsy, multiple sclerosis, and depression and is associated with improved QOL.[30-34]

Rationale for Using Modafinil to Treat Insomnia: To date, the management of Primary Insomnia has focused exclusively on nighttime complaints that are associated with the disorder. The daytime sequelae are considered secondary symptoms that do not warrant direct treatment.

The assumption underlying this approach is that daytime symptoms (e.g., fatigue, sleepiness, and memory and concentration problems, etc.[35,36]) occur as a result of sleep initiation and maintenance difficulties and that they will abate with successful treatment of the primary disorder. The alternative perspective, however, seems worth considering. That is, if patients are provided with treatment so that they function well during the day, they may sleep better at night. Such a strategy, either as monotherapy or in combination with Cognitive Behavioral Treatment, may be useful for the management of insomnia.

NOTE: Study medication was changed from armodafinil to modafinil in an amendment placed to the IRB 5/16/2008 and approved on 6/23/2008.

As Monotherapy: Armodafinil may produce positive treatment effects in several ways. First, the medication may produce an increase in the homeostatic pressure for sleep directly by augmenting the activity of the neurotransmitters associated with wakefulness. Second, modafinil may produce improved sleep continuity by promoting prolonged wakefulness or increased daytime activity. Third, by diminishing the daytime consequences of poor sleep, the medication may diminish the cognitive arousal that is associated with insomnia.

As Part of a Combined Approach: Armodafinil may produce positive treatment effects in two ways. First, subjects may be able to better comply with CBT-I because co-treatment with modafinil may reduce the temporary daytime sleepiness[35,36] and/or worsening of daytime function that accompanies sleep restriction therapy. Second, and perhaps more interesting, subjects may directly benefit from treatment with modafinil as an adjunct to CBT-I. The medication may result in an increase in the homeostatic pressure for sleep, and this increase in sleep pressure may be similar to, and compatible with, behavioral treatments, such as sleep restriction. Thus, one might expect an additive or multiplicative effect when the two treatment modalities are combined.

Summary: We propose to study CBT-I and armodafinil in a four-arm, randomized, controlled, clinical trial of 226 cancer survivors with chronic insomnia. The seven-week intervention is designed to determine the efficacy and acceptability of these treatment strategies in reducing insomnia and fatigue and in improving QOL in cancer survivors. Assessments will be made by diary and by questionnaires before, during, two weeks following, and three months following the study intervention.

Modified 2-6-08 12-01-08

The results of this study could provide potentially important new information with clinical, theoretical and methodological applications. Insomnia in cancer survivors is largely unacknowledged by the medical community even though it is approximately twice as prevalent as in the general population. It exacerbates fatigue and diminishes QOL. The efficacy of CBT-I in treating insomnia in cancer survivors needs to be verified, and new treatment options, e.g., armodafinil with or without CBT-I, need to be studied.

2.0 Objectives

Modified 12-01-08

2.1 Primary Objective: To determine if one or more of the intervention strategies (i.e., CBT-I, armodafinil, or both), when compared to a placebo only group, reduce insomnia in cancer patients following the conclusion of chemotherapy and/or radiation therapy.

2.2 Secondary Objectives:

2.21 To determine if one or more of the intervention strategies (i.e., CBT-I, armodafinil, or both), when compared to a placebo only group, reduce fatigue in cancer patients following the conclusion of chemotherapy and/or radiation therapy.

2.22 To determine if one or more of the intervention strategies (i.e., CBT-I, armodafinil, or both), when compared to a placebo only group, improve QOL in cancer patients following the conclusion of chemotherapy and/or radiation therapy.

3.0 Subject Eligibility

3.1 Study Patients Must:

Modified 12-01-08 3.11 Have a diagnosis of cancer.

3.12 Be able to understand written and spoken English

3.13 Be able to swallow medication

Modified 5-23-08 3.14 Have preferred sleep phase between 7:30 pm and 11:00 am

3.15 Be willing to discontinue any medications/OTCs/Herbals for sleep for the 11-week study period

Modified 2-6-08 3.16 Be presumed to be in a state of cancer remission; use of tamoxifen, an aromatase inhibitor, and/or Herceptin is permitted

Modified 12-01-08 3.17 Self-report problems with insomnia for at least three months and that the insomnia began or got worse with the onset of cancer or treatment

Modified 5-23-08 3.18 Have completed chemotherapy and or radiation not less than one month ago.
12-01-08 (Note: Both types of treatment must be completed at least one month ago if patient receives chemotherapy and radiation therapy and there is no outer limit to how long ago treatments were completed.)

3.19 Report insomnia on the SDS-CL at a frequency of at least 3 days a week

3.19.1 Be at least 21 years of age and less than 75

Modified 12-01-08 3.19.2 (Note: The female only gender criterion has been removed)

3.2 Study Patients Must Not:

Modified 12-18-07 1-18-08 12-01-08 3.21 Have ever taken modafinil or armodafinil or had CBT-I therapy. CBT-I therapy for the sake of this protocol will be defined as any cognitive behavioral-based treatment for insomnia that includes a sleep restriction component.

3.22 Have an unstable medical or psychiatric illness (Axis I-current or within the last 5 years)

Modified 1-18-08 12-01-08 3.23 Have a history of seizures or severe headaches, or uncontrolled cardiac disease or hypertension

3.24 Be presently taking an anticoagulant or a corticosteroid

3.25 Have taken amphetamines (e.g., methylphenidate, pemoline [Cylert®] or similar psycho stimulants) within the past 30 days

3.26 Be currently pregnant or nursing

3.27 Have a history of substance abuse, or meet criteria for current alcohol abuse or dependence as assessed by a CAGE test score >=2 or an Alcohol Use Disorders Identification Test (AUDIT) score >=13

3.28 Have surgery planned within the study period

Modified 12-01-08 3.29 Have ever been diagnosed with sleep apnea or have sleep apnea as indicated by endorsing either question 11 (I wake up choking or gasping for air) or question 12 (My bed partner has noticed that I seem to stop breathing) on the Sleep Disorders Symptom Check at the "Often" or "Frequently" level.

Modified 7-23-09 3.29.1 Criterion regarding RLS/PLMs eliminated.

Modified 10-31-07 3.3 Preliminary Screening

3.31 Identification of Patients

Modified 5-23-08 12-01-08 Potentially eligible subjects at Strong Memorial, Highland and Rochester General hospitals will be approached by their physician, either at a regularly scheduled oncology appointment, or standardized letter in the mail. Print advertising may also be done. The initial contact will be used to assess whether the patient has an ongoing problem with insomnia. Patients will be asked to complete a Sleep Disorders Symptom Check list (SDS-CL See Measures Section). If they indicate that they experience problems with initial, middle, or late insomnia (first three items on the checklist) on three or more days per week and do not endorse two or more items associated with other sleep disorders at the "frequently" level, they will be invited to come to our research center for screening to

determine their eligibility for participating in the study. No further data will be collected on this occasion.

3.32 Subjects will have a 30-60 minute screening interview (conducted or supervised by Dr. Matteson-Rusby) with a clinical research coordinator to confirm their eligibility for the study. Informed consent for the study will be obtained prior to screening. During the interview, the subjects complete the following instruments:

Modified 12-01-08

Modified 5-23-08

- A self-report medical history inventory to rule out illnesses that will interfere or interact with treatment
- A self-report medical symptoms checklist
- Inventory of Depressive Symptomatology (IDS)[37]
- Patient Health Questionnaire (PHQ-9)[38]
- The Mini International Neuropsychiatric Interview (M.I.N.I.)[39]
- Pittsburgh Sleep Quality Inventory (PSQI)[40]
- Alcohol Use Disorders Identification Test (AUDIT)[41]
- CAGE[42]
- Insomnia Severity Index (ISI)[43,44]
- ESS/KSS[45,46]

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3.33 These instruments are standard clinical instruments to establish the suitability of prospective patients for CBT-I therapy. High scores on the IDS, PHQ9, and/or probable diagnoses from the M.I.N.I. will denote unstable psychiatric illness. These subjects will be excluded from participation and provided contact information for local area mental health centers. (see 3.36.2) In addition, any positive response on any of the eight questions on the above instruments (one each on the IDS and PHQ9 and six on the M.I.N.I.) that assess suicidality will result in patients being excluded from the study. The CAGE and Audit assess alcohol use and the ISS and ESS/KSS assess sleep.

Modified 5-23-08 12-01-08

3.34 Subjects who "pass" the intake interview will have a clinical chemistries panel (blood) to rule out any acute or unstable medical co-morbidity. The lab work will include profiles to assess renal, liver, thyroid, and hematological parameters. Pregnancy will also be assessed in women of child bearing potential.

3.35 The study investigators (in collaboration with a study physician and/or the patient's physician) will review the lab work results and medical histories to determine if the patients meet the eligibility criteria for inclusion in the study.

Modified 12-18-07 1-18-08

3.36 Ineligible subjects will receive a telephone call explaining why they were not eligible for participation, and (in the instances where appropriate) they are provided with referral information.

3.36.1 Patients who are ineligible after screening due to sleep problems will be given contact information for three area sleep disorders centers.

Strong Sleep Disorders Center

2337 S. Clinton Ave.
Rochester, NY 14618
585-341-7575
Sleep Disorders Center of Rochester
2110 S. Clinton Ave.
Rochester, NY 14618
585-442-4141

Sleep Insights
10 Hagen Dr., Suite 200
Rochester, NY 14625
585-385-6070

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3.36.2 Patients who are ineligible after screening due to suicidality will immediately be given contact information for five area community mental health centers and referred to their primary care physicians.

DePaul Community Services
1931 Buffalo Rd
Rochester, NY 14624
585-426-8000

Park Ridge Mental Health Center
1561 Long Pond Rd., Suite 117
Rochester, NY 14626
585-723-7450

Genesee Mental Health Center
224 Alexander St
Rochester, NY 14607
585- 922-7770

Unity Mental Health Center
81 Lake Ave
Rochester, NY 14608
585- 368-6900

Strong Behavioral Health
Ambulatory Psychiatry Services
300 Crittenden Blvd # G9054
Rochester, NY 14642
585-275-3535

3.36.3 Patients who are ineligible after screening due to current medical problems will be referred to their primary care physician.

4.0 Randomization

4.1 Patients who meet the eligibility criteria and who have signed the informed consent form will be randomized to one of four trial arms. A computer generated randomization schedule with block size 8 will be used to assign subjects to:

Modified 11-07-07 5-23-08

Arm 1: Placebo P.O. daily/47 days
Arm 2: Armodafinil P.O. daily/47 days (3-days at 50mg, then 40 days at 100mg, then 4 days at 50mg)
Arm 3: CBT-I + Placebo P.O. daily/47 days
Arm 4: CBT-I + Armodafinil P.O. daily/47 days (3-days at 50mg, then 40 days at 100mg, then 4 days at 50mg)

Modified 2-11-08 12-01-08

4.2 Randomization will be stratified by gender.

4.3 A total enrollment of 226 patients is planned

5.0 Treatment Protocol

Modified 12-01-08

5.1 This will be double-blind, placebo-controlled, four-arm clinical with 226 cancer survivors who will be randomized to one of four treatment conditions (CBT-I, armodafinil, both, neither). The seven-week intervention is designed to determine the efficacy and acceptability of these treatment strategies in reducing insomnia and fatigue and improving quality of life in cancer survivors. All ancillary treatments as appropriate for control of symptoms caused by the cancer or its treatment may be administered as clinically indicated.

5.2 Withdrawal of Sleep Medications

All participants, prior to beginning the baseline data collection phase of the study, must have withdrawn from all sleep medications, including: prescription, over-the-counter, CAM and herbal remedies for at least one week prior to beginning the study. Subjects currently taking sedative hypnotics who wish to participate in the study will be withdrawn from medication, under the supervision of their prescribing physician, using a recommended downward titration protocol (1/2 the dose use for 1 week, intermittent use for next week [3 pills prn], no use the third week), before beginning the study. As hypnotic use is a standard of care for insomnia and we are asking subjects to withdraw off this treatment for purposes of the study, this issue will be addressed at time of informed consent. To facilitate this withdrawal process, all patients who wish to participate in the study and are presently taking prescription hypnotics will be asked to sign a release of information so that their prescribing physician can be notified of their

interest in the study, the requirements of the protocol, and the titration process can be initiated by the prescribing physician.

5.3 Initial Questionnaires

Modified 5-23-08 12-01-08 Two weeks of baseline data, prior to randomization, will be collected on patients who meet the eligibility criteria and provide written informed consent, (See schema above and measures section below for details on assessments.) The baseline measures include the ISI, BFI, ESS/KSS, FACIT, PHQ-9, GODIN, Medical Symptoms, Medications and daily diary. For patients needing to withdraw from sleep medication, the daily diary will start when they have completely withdrawn from medication.

Modified 12-01-08 5.4 (Note: The Screening Polysomnography (PSG) has been removed.)

5.5 Treatment Arms

Modified 10-31-07 11-07-07 5-23-08 5.51 Armodafinil (Arms 2 & 4) and Placebo (Arms 1& 3): All patients, according to the randomization schedule, will receive seven weeks of study medication starting on Monday of Study Week 3 (following the 2 week baseline) and will discontinue medication after Friday of Study Week 9 (a total of 47 days). Patients and all research personnel, with the exception of the study pharmacist and the study statistician who will oversee randomization, will be blind to randomization Assignment. Medication will be packaged in four foil packs containing individual daily doses. The first three foil packs will contain 14 daily doses (28 pills) and the fourth will contain 5 daily doses (10 pills). Each daily dose will have two pills with one being labeled a morning dose and one labeled an afternoon dose. The daily doses on the four cards will be labeled Days 1-14, Days 15-28, Days 29-42, and Days 43-47, respectively. Patients will be instructed to take the morning pill between 7 and 9 AM and the afternoon pill between 12 and 2 PM. All of the morning pills for patients randomized to Arms 2 and 4 will be 50 mg. armodafinil. To allow for an upward titration of the study medication, the first three afternoon pills (Days 1-3) will be placebo. For the next 40 days, the afternoon dose will be 50 mg. armodafinil. To allow for a downward titration of the study medication, the afternoon pill on the final four days (i.e., 44 – 47) will be placebo. The pills for patients randomized to Arms 1 and 3 will all be placebo. Patients will be instructed not to use alcohol or take any medications not previously prescribed by their physician. If a participant discontinues study medication, due to unacceptable toxicity or for any other reason, it will not be restarted. Upon notifying study personnel, patients will be allowed to skip the afternoon dose of the study medication or take it prior to 12:00 noon if they believe the afternoon dose of the study medication is making it harder to fall asleep at night.

Modified 11-07-07 5-23-08 Patients will receive their study medication at the time of randomization. The study medication will be dispensed by a clinical research coordinator (CRC) who will be blind to the subject's group assignment. Patients will be required to return to our research laboratory one month after randomization to assess their vital signs as well as any changes in health status and medications. They will also be asked to bring their first two medication cards. The CRC will reiterate the

prescription instructions and note whether the subject has been compliant, both by asking the patient and doing a pill count. In the cases where non-compliance is evident, the CRC will alert the study investigators who will then determine what, if any, further action is required. Unused medication will be returned to the research pharmacy.

Modified 12-18-07

5.52 CBT-I (Arms 3 & 4): CBT-I will be provided on an individual basis to all patients in study Arms 3 & 4 by a licensed clinical psychologist trained in CBT-I. Subjects in these two study arms will receive 7 weeks of CBT-I, using a structured research grade protocol developed at the UR-SNRL. This manualized intervention, which exists as a published text: Perlis et al., 2005, includes four essential components: Sleep Restriction Therapy, Stimulus Control Instruction, Sleep Hygiene Guidelines, and a session of cognitive therapy. The schedule below gives an overview of the CBT-I treatment plan.

CBT-I Treatment Schedule
Session 1: 45 to 90 minutes (Case Review,Sleep Restriction and Stimulus Control Therapy) Durring this session the therapist reviews the case details and baseline sleep diary data from the 1-2 week interval prior to the in-lab study. This information sets the parameters for the sleep restriction therapy and is used to guide the patient toward the treatment to be perscribed. Our standard approach is interactive/didactic. Durring the course of this session, the clinician explains in detail the rationale and procedures for sleep restriction and stimulus control therapy.
Session 2: 30 to 45 minutes (Sleep Hygiene and Sleep Restriction Therapy Adjustments) As with all sessions, sleep diary data are reviewed and charted. The upward titration process for sleep restriction therapy is initiated and sleep hygiene instructions are reviewed
Session 3 & 4: 30 to 45 minutes (Sleep Restriction Therapy Adjustments) Sleep diary data are reviewed and charted. Upward titration is continued.
Session 5: 45 to 60 minutes (Sleep Restriction Therapy Adjustments and Cognitive Restructuring) Upward titration is continued and the cognitive component of the treatment regimen is initiated. In our CBT protocols this involves a Barlow-style approach to "decatastrophization." That is, we addressed the perception of dire consequences of sleep loss, using a form of cognitive restructuring.
Sesion 6: 30 to 45 minutes (Sleep Restriction Therapy Adjustments) Sleep diary data are reviewed and charted. Upward titration continues.
Session 7: 45 to 60 minutes (Sleep Restriction Therapy Adjustments and Relapse Prevention) Relapse prevention issues are reviewed. Typically, this entails a review of: 1) "how insomnia gets started" and the behaviors that maintain poor sleep and 2) the strategies that are likely to bring about and extend episodes of insomnia.

Modified 5-23-08

5.52.1 Patients receiving CBT-I, in addition to completing the normal weekly study questionnaires, e.g., ESS/KSS, ISI, BFI, FACIT, PHQ-9, GODIN, and Medical Symptoms, will also be asked to complete a weekly medication log. The medication log is part of the standard monitoring procedures that are done in our unit when providing CBT-I and it, along with the other weekly measures will insure that the treatments 1) are provided based on the prospective monitoring of

treatment effects and 2) do not significantly exacerbate depression or cause excessive sleepiness. These data are also used to identify adverse reactions or events that are not explicitly reported by the patient. If a steady increase (> 3 weeks) or a sudden increase (> 50% than prior week) in symptoms is observed, an immediate case review (within 2 hours) will be initiated with study medical personnel to determine if the subject requires immediate care and/or should be withdrawn from the study.

5.52.2 Patient Adherence to Protocol. Ultimately, CBT-I is only effective to the extent to which the patient engages in the prescribed behaviors of the Sleep Restriction and Stimulus Control Therapy. These behaviors include:

- delaying bedtime until the appointed time (despite fatigue and sleepiness),
- leaving the bedroom during the night for the wake-after-sleep-onset time intervals that occur during the sleep period (despite the discomfort of leaving the bed and the sensation that "rest is better than nothing"),
- ending the sleep period at the appointed time (despite the potential for sleep loss), and
- not napping (despite the desire to compensate for sleep loss at night).

Modified 12-01-08

5.52.3 Treatment will be provided at the University of Rochester Sleep and Neurophysiology Research Laboratory where a clinical office space is appointed with the necessary therapeutic tools. Note: As a way of reducing patient burden, four of the CBT-I sessions will be conducted by phone instead of in person.

5.52.4 In order to ensure that the protocol is conducted according to specification, the therapist, when providing active treatment, will use a checklist to guide him/her during the conduct of the session. The checklist will remind the clinician of what tasks are required for each session. (Note: As CBT-I sessions will no longer necessarily be done in the University of Rochester Sleep and Neurophysiology Research Laboratory, videotaping of the sessions has been removed.)

Modified 2-6-08 and 12-01-08

5.5B Information Regarding Insomnia Given to Patients in the Placebo Only and Armodafinil Only Conditions:

Patients randomized to either of these conditions will receive the same sleep hygiene guidelines provided to patients in the CBT-I conditions. These include instructions to keep one's bedroom cool and free of light and noise, to go to bed at the same time and get out of bed at the same time each day, to avoid naps, and to avoid using alcohol as a sleep aid.

5.6 Gratis CBT-I for Patients in the Placebo Only and Armodafinil Only Conditions:

Subjects enrolled in the placebo only (Arm 1) and the armodafinil only (Arm 2) arms of this study may, if they so desire, receive treatment for their insomnia using CBT-I following their discharge from the research protocol (week 25). This follow-up care is provided at no cost to the subject.

5.7 Data Collection During and Following the Intervention Phase of the Study

Modified 5-23-08 12-01-08

Patients will complete assessments i.e., ESS/KSS, ISI, BFI, FACIT, PHQ-9, GODIN, and Medical Symptoms every Friday during weeks 3-11 of the study and again during weeks 23 and 24. In addition, the IDS will be completed on Fridays during weeks 9, 11, and 24 and patients will complete the PSQI, medication log, and feedback questionnaire on Fridays during weeks 11, and 24.) A follow-up call by study personnel will be made to each participant not currently receiving CBT-I on each of these Fridays to promote compliance, prompt completion, assess potential side effects of study medication, and answer patient questions. Study participants will also be required to maintain a daily sleep diary for the initial 11 weeks of the study (i.e., baseline, intervention, and post period) and for two weeks at follow-up (Weeks 23 and 24).

Modified 5-23-08 5.8 Adverse Events

5.81 An **adverse event** (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

5.82 A **serious adverse event** (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.

- Is a congenital anomaly/birth defect.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

5.83 An **unexpected adverse event** is any drug experience, the specificity or severity of which is not consistent with the risk information described in the investigators brochure or general investigational plan (see section 5.91). Unexpected as used in this definition refers to an adverse drug event that has not been previously observed rather than from the perspective of such experience not having been anticipated from the pharmacological properties of the drug.

5.85 Adverse Event Reporting

5.84.1 **FDA reporting –** Any adverse event associated with the use of the drug that is both serious and unexpected will be reported to the FDA as soon as possible but no later than 15 calendar days after the initial event. Notification will be submitted via FDA Form 3500A. The FDA shall also be notified by fax or telephone of any **unexpected fatal or life-threatening experience** as soon as possible but no later than 7 calendar days after the event.

5.84.2 **University of Rochester Medical Center Reporting** - Serious adverse events that are associated with the study and occur while a subject is on study until 14 days after the date the subject goes off study must be reported in writing to the Strong Memorial Hospital IRB within 10 working days. They are also reported to the Data Safety Monitoring Committee within the same time frame. Adverse events that are both **unexpected fatal or life-threatening events** must be reported immediately to the IRB. This same protocol will be used to notify **Rochester General Health Systems (RGHS)** of any adverse events so they may report them to their IRB.

5.9 Data Safety Monitoring Plan

Investigators will conduct continuous review of data and patient safety. The review will include for each treatment arm/dose level: the number of patients, significant toxicities as described in the protocol, dose adjustments, and responses observed. The Investigator will submit twice yearly summaries of this data to the Clinical Trials Monitoring

Committee for review. **Rochester General Health Systems** will receive a copy of these summaries.

Modified 12-18-07 Clinical Trials Data Safety Monitoring Committee: The Director of the Cancer Center delegates responsibility for continued review and monitoring of all clinical trials conducted by the URCC to the Clinical Trials Data Safety Monitoring Committee. This committee provides oversight of study progress and safety by review of accrual and adverse events at annual meetings. Any adverse event requiring expedited review per protocol will be submitted to the Data Safety Monitoring Committee (DSMC) for determination as to whether further action is required. The study PI and the study medical monitor determine if the adverse event requires expedited review. Interim meetings are scheduled, as needed, to address specific issues that require immediate attention to assure patient safety.

The Committee:

a) Reviews assigned clinical trials conducted at the URCC for progress and safety
b) Reviews all adverse events requiring expedited reporting as defined in the protocol
c) Reviews reports generated by the URCC data quality control review process
d) Submits recommendations for corrective actions to the Protocol Review Committee and the PI
e) In general, outcome data is not made available to individuals outside of the DSMC until accrual has been completed and all patients have completed their treatment. At this time, the DSMC may approve the release of outcome data on a confidential basis to the trial PI for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMC's recommendation for general dissemination of results must be reviewed and approved by the DSMC.

List of current DSMC members:

Marvin, Knoeck, RPh	Pharmacist
Kishan Pandya, MD	Medical Oncology
Jane Liesveld, MD	Hematology Oncology/BMT
Barbara Asselin, MD	Pediatric Oncology, DSMC Chair
Yuhchyau Chen, MD	Radiation Oncology
Carol French	Administrative Director, Clinical Trials Office / DSMC Safety Coordinator
Nancy Reminder	Clinical Trials Office, Secretary
Li-Shan Huang	Biostatician

Safety Coordinator: The Medical Director of the Cancer Center Clinical Trials Office appoints the Safety Coordinator. The Safety Coordinator monitors adverse event rates utilizing the URCC Clinical Trials database. If any assigned study has had two or more of the same SAEs reported in a month or more than six of the same SAEs in six months, the DSMC will review the summary of SAEs, discuss events with the Study Chair, and conduct a more detailed

review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required.

The Safety Coordinator:

a) Forwards all adverse events requiring expedited reporting to the Data Safety Monitoring Committee Chair who determines if immediate action is required
b) Maintains a database of all adverse events requiring expedited reporting
c) Insures all reports are available for all meetings of the Data Safety Monitoring Committee
d) Monitors adverse event rates utilizing the URCC Clinical Trials database. Adverse event reporting criteria are listed in section 5.8

5.91 Additional Information on Modafinil

Precautions and Contraindications: Modafinil may cause hepatic enzyme induction, and, thus, increase the metabolism of steroidal contraceptives. Because of the risk of a decrease in contraceptive efficacy, women participating in this study will be instructed that steroidal contraceptives must be used with a barrier method while taking the study drug and for a full cycle after discontinuation of the study drug.

Adverse Effects: The most commonly observed adverse events associated with the use of modafinil that have occurred in controlled US and foreign studies were: headache, upper respiratory infection (cold-like symptoms), nausea, nervousness, anxiety, and insomnia. Although rare, serious skin rashes and hypersensitivity reactions have been reported in association with the use of modafinil in pediatric populations. Although modafinil has not been shown to produce functional impairment, any drug affecting the CNS may alter judgment, thinking, or motor skills.

Patients will be instructed not to use alcohol or take any medications not previously prescribed by their physician. There will be no dose reduction. If a participant discontinues study medication, due to unacceptable toxicity or for any other reason, it will not be restarted. The study blind will not be broken at the conclusion of an individual patient's participation or at any time throughout the duration of study medication therapy for any patient in this protocol, except for medical necessity.

Efficacy and Safety of Modafinil in Reducing Daytime Sleepiness and Fatigue: Modafinil (Provigil®) is marketed in the United States (US) for the management of excessive daytime sleepiness (EDS). The US Drug Enforcement Agency (DEA) lists modafinil as a scheduled medication, but classifies it as a level IV controlled substance. The wakefulness-promoting efficacy of modafinil was originally demonstrated in two nine-week, Phase 3, double-blind, placebo-controlled trials that enrolled a total of 558 narcolepsy patients with excessive daytime sleepiness. Modafinil, as single oral doses of 200 and 400 mg/day, significantly improved both primary endpoints (the Maintenance of Wakefulness Test [MWT] and the Clinical Global Impression of Change [CGI-C]), and secondary endpoints, including the Epworth Sleepiness Scale (ESS)[46,47] and instruments assessing physical and mental health and QOL. Modafinil was generally well tolerated at both 200 and 400 mg/day. During the nine-week, double-blind period, the incidence of

adverse events (>5%) was, for the most part, similar in patients receiving modafinil and in those receiving placebo. Most adverse events were mild to moderate in severity. The most commonly observed adverse events associated with the use of modafinil were: headache, infection, nausea, nervousness, anxiety, and insomnia. The discontinuation rate in modafinil-treated patients was 5%, compared to 2% in placebo-treated patients.

The longer-term efficacy and safety of modafinil has also been assessed for up to 136 weeks of open-label treatment following these two nine-week, double-blind studies. Modafinil doses were 200, 300, or 400 mg/day. A total of 478 patients began open-label treatment. Most patients (54%) were on a 400 mg/day dose of modafinil by Week 2, and, approximately, 75% were on a 400 mg/day dose from Weeks 8 to 136 of the extension. No evidence of tolerance was observed. The efficacy and safety profiles of modafinil reported for the nine-week, double-blind portion of the studies were maintained throughout the open-label extension.

In addition to the treatment of excessive sleepiness associated with narcolepsy, modafinil reduces excessive sleepiness associated with obstructive sleep apnea, shift-work sleep disorder, myotonic dystrophy, and Parkinson's disease. Modafinil has also been shown to reduce fatigue in patients with narcolepsy, multiple sclerosis, and depression and is associated with improved QOL.

5.92 Additional Information on Armodafinil

Modified 5-23-08

Armodafinil is the R-enantiomer of modafinil which is a mixture of the R- and S-enantiomers. Pharmacokinetic studies have shown that the concentration-time profiles of the pure R-enantiomer, which is the longer lasting of the two enantiomers, following administration of 50 mg modafinil or 100 mg armodafinil are nearly superimposable. The two medications are virtually identical clinically when adjusted for the 2 to 1 greater dose level for modafinil. The side effect profile of the two medications appears to be similar and slight difference noted on the package inserts generally favor armodafinil.

6.0 Measures

6.1 **Sleep Continuity** will be assessed subjectively using Daily Sleep/Wake Diaries and weekly administrations of the Insomnia Severity Index (ISI), the Epworth Sleepiness Scale (ESS), and the Karolinska Sleepiness Scale (KSS). In addition, the Pittsburgh Sleep Quality Inventory will be administered at three time points (Pre-Post and Follow-up).

Modified 5-23-08

6.12 The Sleep Diary is a 2-page form (1 page/7 days upon wakening, 1 page/7 days when going to bed) that includes measures of sleep continuity (Time to Fall Asleep, # of Awakenings, Total Duration of Awakenings, Total Sleep Time, Total Sleep Opportunity, and Sleep Efficiency); questions regarding study medication, and alcohol use; and 9 Likert scale items re: stress, alertness, concentration, mood, pain, fatigue and daytime sleepiness. Subjects will also be asked to record

the number of hot flashes experienced during the night. The Sleep Diary requires approximately 5 minutes per day to complete.

6.13 The Insomnia Severity Index (ISI) is a commonly used, 5-item psychometrically validated measure used to rate insomnia as not clinically significant, sub-threshold insomnia, clinical insomnia (moderate), and clinical insomnia (severe).[43,44] The ISI requires approximately 5 minutes per week to complete.

6.14 The Pittsburgh Sleep Quality Inventory (PSQI), a commonly used, 25-item psychometrically sound measure scored for both global severity and subscale scores, will assess sleep initiation and maintenance problems and possible etiologic factors (e.g., pain, nightmares, hot flashes).[40,40] The PSQI requires approximately 10 minutes to complete.

6.15 The Epworth Sleepiness Scale (ESS) is a psychometrically sound, 8-item, validated patient self-report questionnaire that provides a subjective measurement of sleepiness.[46] Patients rate how likely they are to doze or fall asleep under a variety of conditions encountered in daily life.[47] For each hypothetical situation, patients rate their likelihood of dozing or sleeping from 0 = "would never doze" to 3 = "high chance of dozing". The ESS total score ranges from 0 to 24.

Modified 5-23-08

6.16 The Karolinska Sleepiness Scale (KSS) is a commonly used measure of sleepiness on which patients provide indicate their level of sleepiness of a scale from 1 (extremely alert) to 9 (extremely sleepy- fighting sleep).[45]

Modified 5-23-08

6.2 **Fatigue** will be assessed with the Fatigue Subscale of the Functional Assessment of Chronic Illness Therapy-Fatigue and the revised Brief Fatigue Inventory**.**

6.21 The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is a 28-item QOL scale developed specifically for use in cancer clinical trials, along with a subscale of 13 additional questions directly related to the impact of fatigue on daily activities.[48] The FACIT-F requires approximately 10 minutes to complete.

6.22 The revised Brief Fatigue Inventory (BFI) is a 9-item, patient-report instrument with established reliability and validity that we have used in previous studies.[49] The BFI allows for the rapid assessment of fatigue level in cancer patients and identifies those patients with severe fatigue. The BFI requires approximately 5 minutes to complete.

Modified 10-31-07 5-16-08

6.23 The **Medical Symptom Checklist** Patients indicate the presence and intensity of each of 30 symptoms on a five point scale.

6.3 **Quality of Life** will be assessed using the 28-item main scale of the FACIT-F, previously described under the measures for fatigue.

Modified

6.4 **Depressive Symptoms** will be measured with the 30 item Inventory of Depressive

5-23-08 Symptomatology (IDS)[37] and with the Patient Health Questionnaire (PHQ-9).[38] The IDS and the PHQ are widely used in insomnia research for assessment of depression.

6.41 The IDS is a self-report instrument that assess all the criterion symptom domains designated by the American Psychiatry Association Diagnostic and Statistical Manual of Mental Disorders - 4th edition (DSM-IV) (APA 1994) to diagnose a major depressive episode.[37] The measure is sensitive to change, with medications, psychotherapy, or somatic treatments, making it useful for both research and clinical purposes. The psychometric properties of the IDS has been established in many study samples.[50]

6.42 The PHQ-9[38]is a 9-item depression scale which scores each of the 9 DSM-IV criteria as "0" (not at all) to "3" (nearly every day). It has validated for use with a variety of populations. [38,51]

6.5 **Feedback** will be obtained by a questionnaire assessing the usefulness and acceptability of the experimental treatments that is completed by the participants at the end of the study.

Modified 5-23-08 6.6 The PSG assessment has been eliminated

Modified 10-31-07 5-23-08 6.7 FSCL deleted

Modified 10-31-07 6.8 The amount of leisure time spent in physical activity will be assessed using the Godin Leisure Time Exercise Questionnaire (GLTEQ).40 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 0.62.[52] The GLTEQ has also been used successfully in populations of adult cancer patients.[53-56]

7.0 Statistical Considerations

Data Handling and Statistical Considerations

Participants will have the option completing measures using paper and pen, or using an internet data portal (IDP) via a personal computer. If the participant does not have access to a computer or for any reason desires to use the paper forms, we will provide the measures on scannable forms (Teleform) that will be electronically sent to an Access Database upon scanning. After scanning, data is audited visually for errors. While the paper forms will be made available, we will encourage participants to use the IDP for all of the self-report instruments used in this study. The IDP system may be viewed at http://rp001.vistalivedata.com. The program is password secured and is fully HIPPA compliant. The system includes alternative access into the system via FAX or telephony.

Data De-identification and Preparation: After each subject reaches full accrual, a programmer under the supervision of Dr. Tu in the Department of Biostatistics will perform final data cleaning and data preparation for the final data analysis. Biostatistics will send electronic queries to the study coordinator when data are delinquent or fail a logic check. In the case of the latter, the study coordinators will make the correction to the database. All data will be de-identified prior to entry into statistical software.

Modified 5-23-08

In addition to data "cleaning", the randomized treatment groups will be compared to determine if imbalances exist. Variables to be considered include basic demographics (e.g., age, gender, time since completion of treatments, having had chemotherapy vs. radiation therapy, socioeconomic status, years married or living with partner, and # children) and whether patients completed the assessments via the internet data portal or by paper questionnaire. Comparisons of categorical variables will be made using Chi-square analysis (or Fisher's exact test, where feasible). T-tests will be used for continuous variables, and nonparametric analyses will be performed, as appropriate. Potential confounds identified in our comparability analyses will be included in the analytic models described below. In addition, the statistical distributions of all data types will be studied at this early stage of analysis and the potential benefits of data transformations (e.g. logarithmic or square root) for continuous variables investigated.

Statistical Programs: SPSS and SAS statistical packages will be used for data analyses. All statistical tests will be performed at the two-tailed 5% level of significance. Likewise, 95% confidence intervals will be constructed for estimation of effects (e.g., difference in insomnia severity between each of the treatment groups and the placebo only group). Data will be analyzed on an "intent-to-treat" basis; participant data will be included in the treatment group to which the participant was randomized, regardless of whether the subject completes the treatment regimen.

Assumptions and Outliers: The assumptions underlying all statistical analyses will be thoroughly checked using appropriate graphical and numerical methods.[57,58] In the case of serious violations of distribution assumptions such as normality, appropriate nonparametric methods will be attempted.[59,60] If outliers or influential data are detected, the accuracy of the data will be investigated. If no errors are found, analyses may be repeated after removing these cases to evaluate their impact on the results. However, the final analyses will include these data points.

Missing Data: It is anticipated that by allowing for 46 subject drop-outs (20%) and by checking self-report measures for completeness, we will have a full compliment of data. This said, item-level or full scale score missing data will be modeled or interpolated based on adjacent observations or on the basis of individual and/or group trends.

Statistical Analyses: We will use methods for longitudinal data analysis to assess between-group changes over time for each of the primary outcome variable. Treatment condition, time, and time by treatment condition will be included as predictors. We will use piece-wise linear functions of time to model time trend if linear functions prove to be inadequate. For each of the three outcomes: sleep continuity, fatigue, and QOL, an overall test of whether there are differences among the groups will be done first by examining treatment group by time interaction. If overall differences are detected, post-hoc comparisons will be performed to examine specific group differences using appropriate linear contrasts.

Hypothesis 1
All three intervention strategies will, as compared to the placebo only group, improve insomnia in patients, where the largest effects will occur with the combined strategy.

The primary analysis will use severity of insomnia as assessed by the total score of the ISI as the outcome variable. The primary analysis will use longitudinal models with treatment condition, time, and time by treatment condition as predictors and insomnia severity as the dependent variable. We will first examine the treatment group by time interaction to determine if there are overall differences among the groups, and then linear contrasts will be used to compare the groups in pairs. In addition to statistical significance, we will also examine effect size and confidence limits for differences among the treatment groups.

A series of three additional secondary analyses examining this hypothesis will substitute three commonly used sleep continuity variables that correspond to sleep initiation and maintenance in place of the insomnia severity score from the ISI in order to provide a more complete characterization of the effects of the intervention on sleep. These are Sleep Latency (SL), Wake After Sleep Onset (WASO), and Total Sleep Time (TST). Each of these measures will be culled from the daily diaries and will be averaged to represent 1) pre-post comparisons for the two week intervals preceding and following therapy and 2) means for each of the 11 weeks in the present study.

All of the analyses above correspond to our a priori hypotheses. A number of additional analyses are possible. For example, it may be that the three active treatment arms show superior improvements over the placebo when assessed pre to post, but the speed of response differs among conditions. Three ways to assess this might be 1) a latency in day to a criterion response, 2) an area under the curve analyses, and 3) a comparison of the rates of slopes of changes. These kinds of ad hoc analyses will be pursued following our primary and secondary analyses. We will also use recommendations as set forth by Kraemer[61] and Cole and Maxwell[62] to examine whether intervention effects on insomnia mediate intervention effects on fatigue (as assessed by the BFI total score). If positive, these regression analyses would more firmly establish the link between insomnia and fatigue. In addition, since we are assessing fatigue and insomnia every other week, we can begin to see if insomnia affects fatigue or fatigue affects insomnia by looking at the temporal association between fatigue and insomnia in a post-hoc analysis.

Hypothesis 2
All three intervention strategies, as compared to the placebo only group, will reduce fatigue in patients, where the largest effects will occur with the two conditions that utilize armodafinil.

The same modeling strategies as in Hypothesis 1 with the dependent variable replaced by fatigue (as assessed by the BFI total score) will be used. The trend in each group will be assessed by testing the sign of the coefficient of the time variable. Group by group comparisons using appropriate linear contrasts will be used to check if the largest effects occur with two conditions that utilize armodafinil.

As a secondary analysis for this hypothesis, we will repeat the above analysis substituting the fatigue sub-scale score from the FACIT-F in place of the BFI score.

Hypothesis 3
All three intervention strategies, as compared to the placebo only group, will improve QOL patients, where the largest effects will occur with the combined strategy.

The same modeling strategies as in Hypothesis 1 with the dependent variable replaced by QOL (as assessed by the main 28-item scale of the FACIT-F) will be used. Treatment group by time interaction will be used to test if there are overall differences among the groups.

Additional Analyses

Modified 2-6-08 Section on PSG related analyses deleted

Correlational analyses will be used to exam the relationships among insomnia, fatigue, and QOL. We will also correlate changes over time in these variables to characterize how changes in one, e.g., insomnia, relate to changes in the others.

8.0 Records to be Kept

Modified 04-24-08, 5-23-08, and 12-01-08

SCHEDULE OF DATA COLLECTION					
Measure	**At consent**	**Baseline** Weeks 1 & 2	**Intervention** Weeks 3-9	**Post** Weeks 10 & 11	**Follow-up** Weeks 23 & 24
On-Study	X				
Med Hx	X				
CAGE&AUDIT	X				
IDS	X		Week 9 only	Week 11 only	Week 24 only
MINI	X				
PSQI	X			Week 11 only	Week 24 only
Medications		Week 2 only		Week 11 only	Week 24 only
Medical Symptoms	X	X[a]	X[a]	X[a]	X[a]
ESS/KSS	X	X[a]	X[a]	X[a]	X[a]
PHQ9	X	X[a]	X[a]	X[a]	X[a]
ISI	X	X[a]	X[a]	X[a]	X[a]
BFI		X[a]	X[a]	X[a]	X[a]
FACIT		X[a]	X[a]	X[a]	X[a]
GODIN		X[a]	X[a]	X[a]	X[a]
Night Diary		X[b]	X[b]	X[b]	X[b]
Morning Diary		X[b]	X[b]	X[b]	X[b]
Feedback				Week 11 only	Week 24 only

9.0 Patient Consent and Pier Judgment

9.1 Current FDA, ICH, NCI, state, federal, and institutional regulations concerning informed consent will be followed.

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