PENNSTATE

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

A Randomized, Double Blind, Placebo Controlled Evaluation of Modafinil vs Placebo for the Treatment of General Anesthesia Related Delayed Emergence in Patients with the Diagnosis of Obstructive Sleep Apnea.

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Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (http://irb.psu.edu). For all other research, do not delete the instructional boxes from the final version of the protocol.**
5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

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1.0 Objectives

1.1 Study Objectives

To determine the effectiveness of low dose modafinil compared to placebo in improving postoperative recovery in patients with the diagnosis of obstructive sleep apnea. Our hypothesis is that pre-operative modafinil administration will result in a 20% reduction in Post-Anesthesia Care Unit (PACU) length of stay for patients with obstructive sleep apnea recovering from general anesthesia.

1.2 Primary Study Endpoints

Post-Anesthesia Care Unit Length of Stay (PACU LOS): Time from extubation to readiness for discharge from the PACU.

1.3 Secondary Study Endpoints

Time from termination of volatile anesthetic to extubation
PACU stay-related Pain Scores
Narcotic use in PACU
Intraoperative narcotic use
Hospital Length of Stay
Cardiac Morbidity, Mortality
Pulmonary Morbidity, Mortality

2.0 Background

2.1 Scientific Background and Gaps

The perioperative care of patients with obstructive sleep apnea (OSA) continues to be a pressing issue due to increased rates of adverse respiratory events, increased sensitivity to anesthetic related medications, and ultimately delayed anesthetic recovery. This study seeks to assess the use of pre-operative modafinil, an FDA approved psychostimulant drug indicated for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea, or shift work disorder, in decreasing the incidence of delayed anesthetic recovery. In contrast to traditional psychostimulants, modafinil has a lower incidence of side effects[1]. Chronic use is associated with a low frequency of adverse cardiovascular events[2], negligible systemic sympathomimetic activity and is associated with a low potential for abuse[3, 4].

2.2 Previous Data

In small trials, modafinil has demonstrated effectiveness in improving recovery from general anesthesia in a generalized population[4] but did not improve patient psychomotor skills after sedation in another trial[5].

2.3 Study Rationale

Clinically, modafinil has demonstrated effectiveness in narcolepsy and shift work sleep disorder. Modafinil demonstrated significant clinical effectiveness as measured by subjective and objective measures of wakefulness in several large randomized, double blind, placebo controlled studies in patients with narcolepsy[6,7]. Several open label investigations have determined that for the indication of

narcolepsy, the drug was well tolerated with no evidence of significant events or abuse. Modafinil was also shown to be effective for shift worker sleep disorder with improvements in sleep latency, vigilance, and sleep related function[8]. Modafinil was found to be effective for daytime somnolence associated with obstructive sleep apnea in patients who are regular users of nasal continuous positive airway pressure therapy[9,10]. Other than the above referenced studies, there is a paucity of meaningful research on the use of modafinil in the perioperative setting.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. 18 years or older
2. Meets diagnostic criteria for obstructive sleep apnea
3. Willing and able to comply with study procedures
4. Willing and able to provide informed consent
5. If female, not pregnant or lactating and willing to use an acceptable method of barrier birth control (e.g. condoms) for one month after surgery and discontinuation of study medication (modafinil may reduce the effectiveness of steroidal contraception for one month after discontinuation).
6. Elective surgery with anticipated general endotracheal anesthesia management.
7. Able to speak, read and write English

3.2 Exclusion Criteria

1. Have a medical condition that, in the study physician's judgment, may interfere with safe participation (active cardiac conditions such as angina, recent myocardial infarction w/in 6 months, severe renal or liver disease, unstable diabetes, or elevated liver enzymes greater than twice normal).
2. Have a current neurological disorder (e.g. organic brain disease, dementia) or major psychiatric condition that would impair the collection of data (schizophrenia, bipolar illness).
3. Currently on prescription medication that is known to interact with the study drug. (ethinylestradiol and triazolam).
4. Have current dependence on cocaine, methamphetamine, alcohol or benzodiazepines (DSM-IV criteria).
5. Have a history of severe valvular heart disease, severe left ventricular hypertrophy, cardiac arrhythmias, angina, cardiac syncope, or pre-syncope or myocardial infarction <6 months.
6. Have a history of uncontrolled or poorly controlled essential hypertension, or a heart rate greater than 70% of the maximum heart rate expected for their age (Formula: 0.70(220 – age).
7. Any condition, in the opinion of the principal investigator that would compromise patient safety.
8. A documented history of sensitivity to modafinil.
9. Current or recent use of <48 hours of modafinil use for daytime somnolence associated with obstructive sleep apnea.
10. Current pregnancy
11. Cognitive impairment

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

1. Inability or refusal to continue in the study
2. Newly diagnosed pregnancy, or refusal and/or inability to reliably use barrier contraception for one month after administration of study drug.

3. Newly diagnosed cardiac, neurological, or pulmonary disease on day of surgery.

3.3.2 Follow-up for withdrawn subjects

Patients will be withdrawn from the study prior to start of procedure. Patients will receive a call or visit from the principal investigator to determine cause and will document.

4.0 Recruitment Methods

4.1 Identification of subjects

Patients will be recruited prior to their visit in the Pre-Anesthesia Clinic clinic. As an alternate location, room C2832 may also be used. The research team will review the patient's pre-operative history for their elective surgery to determine if that the patient meets the research study inclusion/exclusion criteria.

4.2 Recruitment process

After a potential patient is identified, and initial telephone contact is made, they will be given the Patient Information Sheet related to the study at the time of their Pre-Anesthesia Clinic visit. If, after reading about the study, the patient continues to express a willingness to participate, a research team member will review the consent document and answer all questions prior to obtaining informed consent from the subject. As per standard of care, patients of childbearing age will receive a pregnancy test on the day of surgery. If the pregnancy test results in a positive reading, the patient will be removed from the study. If initial phone contact is made and patient is amenable to research study enrollment, day of surgery consent may be obtained in Same Day Unit (SDU). This is necessary to include patients not receiving a pre-op visit within the main medical center.

4.3 Recruitment materials

Please see the attached plain language "Patient Information Sheet" document in CATS.

4.4 Eligibility/screening of subjects

See Sections 4.1 and 4.2 above.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Informed consent will occur after their regularly scheduled appointment in the Pre-Anesthesia Clinic. If patient is not receiving a pre-op visit within the medical center, day of surgery consent may be obtained in the Same Day Unit (SDU).

5.1.1.2 Coercion or Undue Influence during Consent

Study procedures will be fully explained, voluntariness will be emphasized as well as the fact that no care will be denied regardless of the subjects decision.

5.1.2 Waiver or alteration of the informed consent requirement

A waiver of consent is requested to review subject records to determine eligibility. The eligibility review will minimize the number of screen failures.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Written documentation of consent will be obtained. A signed copy will be given to the participant, one will be retained by the study team and one will be uploaded to the patient medical records.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)

Not applicable as we will be obtaining full written consent.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Patients that are not able to speak, read and write English, will not be included in the study.

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Cognitively impaired patients will not be included in the study.

5.3.2.2 Adults Unable To Consent

Patients unable to provide informed consent will be excluded from this research study.

5.3.2.3 Assent of Adults Unable to Consent

Not applicable.

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission

Not applicable.

5.3.3.2 Assent of subjects who are not yet adults

Not applicable.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

At the conclusion of the data collection, after data analysis, patient identifiers will be destroyed.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

PHI will be used to assess patients for study eligibility.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The waiver is requested only for recruitment to determine subject eligibility to ensure that no medical conditions that fall into the exclusion criteria are present and would thus preclude enrollment. This waiver will minimize the enrollment of subjects' who may ultimately fail to meet the study inclusion/exclusion criteria.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

Double blind, randomized, controlled study examining preoperative administration of modafinil in patients with the diagnosis of obstructive sleep apnea undergoing general anesthesia.

7.2 Study Procedures

7.2.1 Pre- Anesthesia Clinic Visit:

Patients meeting the inclusion/exclusion criteria will be gauged for interest in participating in the clinical trial. If the patient is amenable to participation, informed consent will occur after their appointment in the Pre-Anesthesia Clinic. At the time of consent, vital signs will be collected from the standard of care medical record information. As per standard of care, patients of childbearing age will receive a pregnancy test on the day of surgery. If the pregnancy test results in a positive reading, the patient will be removed from the study.

7.2.2 Day of Surgery:

Research Randomization and Oral Administration of Study Drug: On the day of elective surgery, preoperatively, the patient will be assessed for any changes in health status since the preoperative clinic visit. If any contraindications are met (see exclusion criteria), the patient will be removed from the study and will proceed with their surgical procedure at the discretion of the attending surgical and anesthetic team. If no exclusion criteria have been met, the patient will be randomized, by the Investigational Drug Service Pharmacy, to receive placebo or modafinil, 200mg. The research team and the subject will both be blinded to what agent is received. Patients will receive the study drug by mouth with one ounce of water, approximately 15-30 minutes prior to general anesthesia.

General Anesthesia and the Surgical Procedure: Both procedures will proceed at the discretion of the surgical and anesthetic team with the following criteria. Preoperatively, patients will not receive midazolam prior to anesthesia induction. Intraoperatively, patients will have inhalational anesthesia (sevoflurane or desflurane) titrated to a MAC (minimum alveolar concentration) of 0.8-1.2, unless clinically indicated. Mean arterial pressure will be maintained within 20% of baseline mean arterial pressure, unless clinically indicated. No gastric suctioning will occur for sixty minutes from time of test article ingestion, unless clinically indicated.

Patients that receive gastric suctioning prior to sixty minutes will be removed from the study protocol. The Bispectral Index will be monitored and recorded at fifteen minute intervals from the start of the anesthesia procedure to extubation. The time from the termination of inhalational agent to extubation will be measured as a secondary outcome measure. No other recommendations or restrictions are in place for the care of the patient, and the anesthesia and surgical teams will proceed with usual practice for the care of the patient.

Post Procedural Research Data Collection: Upon extubation, the patient will be transported in the usual fashion to the PACU. The PACU nurses will follow standard of care practices in caring for the patient. Time from extubation to readiness for discharge from PACU will be recorded as the primary outcome. At one hour after extubation time, vital signs will be recorded by a member of the research team. Upon fulfilling discharge criteria, the patient will be discharged to an inpatient unit or home. At the conclusion of the patient's care in the hospital, a physician co-investigator will review the patient's electronic medical record specific to that admission to record documented perioperative complications.

7.2.3 Follow-up:

2 weeks after the day of surgery (± 2 days), a follow up phone call will be performed by a member of the research team to assess for patient satisfaction and delayed complications.

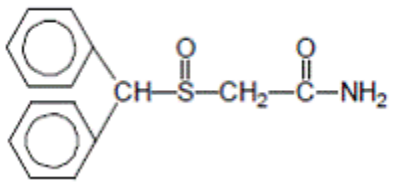
7.3 Duration of Participation

The subject's participation in the study will begin on the day of their Pre-Anesthesia Clinic visit and continue through the follow-up phone call 2 weeks (± 2 days) after the day of surgery. The total duration will be approximately 3-6 weeks.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

Modafinil, an FDA approved atypical psychomotor stimulant, will be utilized in the interventional arm of this study. Provigil (modafinil) is a wakefulness-promoting agent for oral administration. Modafinil is a racemic compound. The chemical name for modafinil is 2-[(diphenylmethyl)sulfinyl]acetamide. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.35.
The chemical structure is:



Modafinil is a white to off-white, crystalline powder that is practically insoluble in water and cyclohexane. It is sparingly to slightly soluble in methanol and acetone. Modafinil tablets contain 200 mg of modafinil and the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and pregelatinized starch.

Provigil (modafinil) is FDA approved for the following indications: to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, or shift work disorder. In obstructive sleep apnea, modafinil is indicated to excessive sleepiness

and not as a treatment for the underlying obstruction. Maximal therapy with CPAP for an adequate period of time should be made prior to initiating and during treatment with modafinil for excessive sleepiness.

Modafinil has been evaluated for safety in over 3500 patient, of which 2000 patients were treated for excessive sleepiness associated with obstructive sleep apnea, shift worker disorder, and narcolepsy. In placebo controlled studies, the most common adverse reactions (>5%) were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness and dyspepsia. Rare events of angioedema, anaphylaxis, multi-organ hypersensitivity reactions have been reported. Serious rash was reported <0.8%, and onset occurred within 1-5 weeks on initiation of chronic therapy with modafinil. Notable drug interactions include warfarin (patients require additional monitoring with concomitant therapy), antidepressants (elimination may be increased in patients concomitantly administered tricyclic antidepressants and selective serotonin reuptake inhibitors.

FDA approved Modafinil 200mg Tablets will be obtained for use in this study.

7.4.2 Treatment Regimen

The recommended dosage for patients with narcolepsy or obstructive sleep apnea is 200 mg taken orally once a day as a single dose in the morning. Doses up to 400mg/day, given as a single dose, have been well tolerated but there is no consistent evidence that this dose confers additional benefit beyond that of the 200mg/day dose. In this study, the interventional arm will be receiving 200mg Modafinil immediately prior to their surgical procedure.

7.4.3 Method for Assigning Subject to Treatment Groups

The Public Health Service statistician will generate a randomization list for the study. This will be securely transferred to the Investigational Drug Services Pharmacy for incorporation in the dispensation of the test article or placebo as per protocol.

7.4.4 Subject Compliance Monitoring

Not applicable

7.4.5 Blinding of the Test Article

Active Modafinil 200mg tablets and matching placebo capsules will be compounded by the Investigational Drug Service Pharmacy according to applicable protocols. Active Modafinil 200mg capsules will be prepared by placing a commercially available 200mg Modafinil tablet and methylcellulose into a size 00 empty gelatin capsule. Matching placebo capsules will be prepared by placing methylcellulose into a size 00 empty gelatin capsule. Placebo will be generated to have the same consistency, texture and shape of the active drug. The research pharmacy will dispense the medication, ensuring that patient, clinical care and research teams are blind to the intervention.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

Test article will be purchased by the Penn State Hershey Medical Center Investigational Drug Service Pharmacy (Room PG200 M.C.CH79, Penn State Hershey Medical Center, 500 University Drive, Hershey PA 17033). Ordering of

the test article will be conducted by the Investigational Drug Service Pharmacy and commercially available Modafinil 200mg tablets will be purchased through Cardinal Health™. Empty gelatin capsules and USP-grade methylcellulose will be purchased from approved pharmacy vendors. Compounded capsules, Modafinil tablets, methylcellulose, and empty gelatin capsules will be stored in the Investigational Drug Service Pharmacy at controlled room temperature, labeled with the strength, compounded capsule lot number, expiration date and protocol number. Personnel responsible for ordering of study products will establish a procedure to ensure that sufficient drug supply is available for the duration of the study. Both modafinil and placebo will be compounded on site, randomized and dispensed by a qualified pharmacist associated with the research pharmacy. There will be one capsule containing study drug (200mg modafinil) or placebo. This will transported to the patient in the preoperative area by a member of the research team. Chain of custody documentation will be maintained for all personnel involved in the transport and handling of study products, including the person delivering the product and the person receiving the product, as appropriate. The patient will then take the intervention orally with a sip of water prior to surgical procedure.

7.4.6.2 Storage

The Investigational Drug Service Pharmacy will purchase, store and distribute the study medication or placebo according to their approved protocols.
Upon receipt of study product, the Investigational Drug Service Pharmacy or designated individual will ensure that the information on the packing slip matches the test article. The recipient will verify product identification, amount of product received, lot numbers, expiration date, physical condition and that storage conditions have been maintained. The recipient will notify the supplier of receipt and condition of the study products, according to the product supplier's specified instructions. If there any discrepancies discovered upon receipt of the test article, the supplier and principal investigator will be promptly notified.

The principal investigator is ultimately responsible for ordering and accountability of all study products in his/her investigational trial, the investigational drug service pharmacy shares this responsibility when it accepts/receives the study product. All test articles supplied for this protocol will be accounted for utilizing a written manual or electronic accountability log. If an electronic accountability log is used, it must have a verifiable audit trail. Accountability of test article must be documented from the time of initial product receipt, dispensation and final disposition of study product. Each time a test article is dispensed to a subject, received from the supplier or other source, returned, destroyed or transferred to another study, the occurrence shall be recorded on the accountability log. This log should indicate amounts received from the supplier, delivered/dispensed to the subject, returned to the supplier, disposed or destroyed, as appropriate per the protocol. Subject dispensing must be compared with drug accountability logs for consistency to ensure that all subjects scheduled to receive a study product are enrolled in the study. Physical inventory of the test article must be conducted at minimum of once quarterly to confirm that quantity on hand is consistent with the inventory balances on the accountability log. This procedure includes a cross check of

drugs in stock with the amount recorded on the drug accountability log and a check of expiration dates, preparation dates and lot numbers. Discrepancies between the accountability records and the physical quantity on hand will be reviewed and reconciled by the Investigational Drug Service Pharmacy and a written report submitted to appropriate parties.

The study specific supply of medication will be stored in the Investigational Drug Service Pharmacy at controlled room temperature. Continuous wireless temperature monitoring occurs in the Investigational Drug Service Pharmacy.

7.4.6.3 Preparation and Dispensing

Upon receipt of a study specific order and confirmation of consent, the Investigational Drug Service Pharmacy will consult the randomization list to obtain a subject's treatment assignment. The dose will be prepared and labeled as "IDS Modafinil 200mg/Placebo Study Tablet". Once the dose has been prepared, the pharmacist or designated personnel will dispense the prepared patient study dose to the study team or the patient's nurse for patient administration. The test article will then be delivered to the patient in the preoperative area of the Penn State Hershey Medical Center by an available member of the research team. It will be dispensed to the patient with one ounce of water for consumption prior to general anesthesia.

7.4.6.4 Return or Destruction of the Test Article

Test article disposal at the end of the study will be deferred to the Investigational Drug Service Pharmacy for determination of feasibility of destruction on site, transferal to a different protocol or return to drug manufacturer according to current protocols. Any dispensed doses that are not administered must be returned to the Investigational Drug Service Pharmacy. These doses will then be destroyed as per the HMC Investigational Drug Destruction Policy. Any expired study medications or supplies will be destroyed as per the Investigational Drug Destruction Policy. At study completion, study supplies will not remain at the site unless otherwise specified in the protocol.

7.4.6.5 Prior and Concomitant Therapy

No prior and/or concomitant medical therapy will be collected. All concomitant medications are permitted during the study.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

120 subjects will be recruited for this clinical study. As noted above, this number accommodates a 10% dropout rate.

8.2 Sample size determination

We believe a difference of 45 minutes with respect to time from extubation to readiness for discharge from the PACU (PACU length of stay) would be clinically meaningful. Based on a previous study, we anticipate the standard deviation for this outcome to be 70 minutes and that the outcome will be skewed (i.e., not normally distributed). Given these assumptions, a sample size of 54 subjects per

treatment group will provide 90% statistical power to detect a difference of 45 minutes between the two treatment groups, assuming a standard deviation of 70 minutes, using a two-sided Mann-Whitney test with a significance level of 0.05. We conservatively anticipate a subject drop-out rate of 10%; therefore, we will randomize a total of 120 subjects for the trial.

8.3 Statistical methods

A Mann-Whitney test will be used to compare the two treatment groups with respect to the primary outcome of the time from extubation to readiness for discharge from the PACU (PACU length of stay) because we anticipate this outcome to not be normally distributed. In the event that the primary outcome is normally distributed, a more powerful two-sample t-test will be used to compare the treatment groups. Secondary continuous outcomes (e.g., time from termination of volatile anesthetic to extubation, PACU stay-related pain scores and hospital length of stay) will be compared between the two treatment groups using two-sample t-tests or Mann-Whitney tests as appropriate based on the normality of their distributions. Secondary binary outcomes (e.g., narcotic use in PACU, intraoperative narcotic use, cardiac morbidity and mortality, and pulmonary morbidity and mortality) will be compared between the two treatment groups using a chi-square test or Fisher's exact test as appropriate. At approximately patient 40 and 80, blinded statistical analyses will be performed by the statistician to ensure an accurate power analysis.

9.0 Confidentiality, Privacy and Data Management

Please see Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review.

10.2 Data that are reviewed

The data to be reviewed will be:

- Safety data
- Untoward events
- Efficacy data

10.3 Method of collection of safety information

Safety information will be collected by the research staff preoperatively, post operatively and two weeks following surgery as described in Section 7.2.

10.4 Frequency of data collection

Data will be collected on the day of surgery, and the telephone follow-up 2 weeks (±2 days) later.

10.5 Individuals reviewing the data

Oversight for the conduct of the study will be provided by the PI and the research coordinator will monitor the data. They will ensure that all eligible criteria and consent requirements are met prior to a subject's participation in the study and that the procedures and adverse event reporting occur according to the IRB approved protocol.

10.6 Frequency of review of cumulative data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review.

10.7 Statistical tests

Not applicable

10.8 Suspension of research

Intraoperative Mortality not directly attributable to surgical or anesthetic procedures will terminate the study. Any evidence of cardiac or pulmonary morbidity directly attributable to use of the study drug will terminate the study.

11.0 Risks

Loss of confidentiality

Risk of randomization

Reasonably foreseeable risks of chronic modafinil administration in the perioperative time period as per pooled placebo controlled trials in Narcolepsy, Obstructive Sleep Apnea, and Shift Worker Disorder. All less than 5% unless otherwise noted. There is no significant data for single use in the perioperative time period.

- Headache (34%)
- nausea/emesis (11%)
- increased anxiety/nervousness (7%)
- Rhinitis (7%)
- Back Pain (6%)
- Diarrhea
- Dizziness
- Insomnia
- Anorexia
- Pharyngitis
- Hypertension
- Chest Pain
- Constipation
- Depression
- Palpitations
- Paresthesia
- Somnolence
- Tachycardia
- Vasodilation
- Abnormal Vision

- Agitation
- Asthma
- allergic/hypersensitivity reaction
- Pregnancy Category C – Intrauterine growth restriction and spontaneous abortion have been associated with modafinil and armodafinil have been reported.
- Nursing Mothers: It is not known whether modafinil or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Modafinil is administered in nursing females.
- Serious but rare side effects include:
  - Stevens-Johnson Syndrome
  - Tachyarrhythmia
  - Allergic Reaction (Anaphylaxis)

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

Potential benefits:
Individual Patient

a. Potential reduction in PACU length of stay
b. Potential reduction in overall length of stay
c. Potential reduction in patient perioperative risk: risk reduction in centrally mediated respiratory depression
d. Improvement in overall patient centered wellbeing after surgery

12.2 Potential Benefits to Others

Potential benefits:
General Anesthesiology Practice

a. Decreased perioperative risk of centrally mediated respiratory depression (a known safety risk factor in patients with the diagnosis of obstructive sleep apnea)
b. Improved PACU throughput of patients with the diagnosis of obstructive sleep apnea.
c. Reduction in respiratory related complications associated with obstructive sleep apnea.

Societal benefits:

a. Improved patient safety in at risk patient population
b. Decreased expenditure on respiratory related complications in at risk patient population.

13.0 Sharing Results with Subjects

N/A – results will of the study will have no impact on the clinical care of the patients

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not applicable

15.0 Economic Burden to Subjects

15.1 Costs

There will be no additional costs to the patients for their participation in this research.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Patients will be recruited and study procedures will be performed at the Milton S. Hershey Medical Center, Hershey PA, USA. The principal investigator is Zyad J. Carr, M.D., assistant professor, Department of Anesthesiology. The principal investigator has 5 years of experience in the execution of clinical trials including examining the use of donepezil in schizophrenia, neurocognitive testing of function in the postoperative time period, and basic science research in postoperative cognitive dysfunction.

16.2 Feasibility of recruiting the required number of subjects

Approximately 20,000 surgical procedures are performed at Milton S. Hershey Medical Center per annum. In the general population, approximately 4-11% of the population carries the diagnosis of obstructive sleep apnea. One study has determined that the incidence of obstructive sleep apnea in the surgical patient population is approximately 24%. This implies that approximately 5000 patients with confirmed or suspected obstructive sleep apnea will undergo surgery at Penn State Hershey Medical Center at any one year. This research study seeks to surpass the 2% acceptance rate needed to complete the study in one year.

16.3 PI Time devoted to conducting the research

The principal investigator has protected research time within the confines of his clinical schedule. Several additional clinician investigators will partake in this study. In addition, broad support will be provided by the department of anesthesiology ancillary staff, and dedicated research staff.

16.4 Availability of medical or psychological resources

The principal investigator and research team will, to the best of our collective abilities, attempt to coordinate the patient's care during the surgical and anesthetic procedure and provide access for study related incidents or queries in the postoperative time period up to the 2 week phone survey.

16.5 Process for informing Study Team

Research team training will proceed after IRB approval and will involve the following:

1. One hour training session to obtain qualification on the postoperative recovery scale.
2. One pre-clinical meeting with the preoperative anesthesia clinic to describe the study, answer questions concerning the study protocol and provide contact information.
3. One hour principal investigator led meeting with co-investigators (clinicians) to disseminate information and answer questions concerning the study.

4. Coordination with the research pharmacy.
5. Departmental communication session to disseminate information and answer questions concerning the study protocol.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of the Use of Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload the Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

Not applicable

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate 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.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

19.2 Recording of Adverse Events

Patients will be monitored for the occurrence of Adverse events throughout the surgery and their stay in the PACU.

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy (**NOTE:** Simply

repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.)

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
  The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

Not applicable

19.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

19.6 Unblinding Procedures

The allocation code will be permitted to be broken upon the request of the principal investigator, clinical staff, or trial statistician. Unblinding will be permitted to make clinical treatment decisions in the event of a serious adverse event occurrence believed to have been attributable to the test article, at the request of the Data Safety Monitoring Board and at the conclusion of the study to determine the effect of intervention. The Investigational Drug Service Pharmacy will hold allocation codes for individual subjects, holds the record of randomization, and will unblind the study upon request and according to standard procedure.
Unblinding Protocol
The principal investigator or other parties as described above, in consultation with the clinical team, assess the need for unblinding, and approves unblinding.

- Investigational Drug Service Pharmacy is notified
- Investigational Drug Service Pharmacy completes an unblinding request form.
- Identifies and promptly provides the clinical team of subject allocation as per current protocol.
- Removes the subject from the active clinical trial.

19.7 Stopping Rules

Current study endpoint is not defined as high risk. Patient safety will be continually monitored throughout the study period to determine if stopping rules should be instituted. It is generally agreed that a clinical trial on ethical grounds if;

- Evidence of abnormally elevated cardiopulmonary events based on continuous monitoring during the study duration.
- Evidence of futility of treatment based on ongoing data analysis.
- Clinical team members assessment of intraoperative complications.

It is also well understood that during the conduct of randomized controlled trials, hazard ratios are often unstable with the possibility of significance early in the trial and falling into nonsignificance when examined at the end of the trial[a]. Each major adverse event will be exhaustively examined for possible association with the test article.

a: Nissen SE. ADAPT: The Wrong Way to Stop a Clinical Trial. PLOS one. 2006

20.0 Study Monitoring, Auditing and Inspecting

Not applicable

21.0 Future Undetermined Research: Data and Specimen Banking

Not applicable

22.0 References

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