Title: A Randomized Trial of Positive Airway Pressure Therapy to Treat Cognitive Dysfunction in MS Patients with Obstructive Sleep Apnea

PI: Tiffany Braley, MD, MS

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Institution:	**University of Michigan**
Principal Investigator:	**Tiffany J. Braley, MD, MS**
Co-Investigators:	**Ronald D. Chervin MD, MS**
	Joseph W. Burns, Ph.D
	Anna L. Kratz, Ph.D

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PROTOCOL SUMMARY

Background and Rationale

Multiple sclerosis (MS) is a chronic, autoimmune disease that causes inflammation and destruction of the brain and spinal cord. This condition is the leading cause of non-traumatic disability among young adults, and affects nearly half a million Americans and 2.5 million people worldwide. In addition to physical disability, MS patients suffer disproportionately from a variety of complications that negatively impact quality of life, including cognitive dysfunction, and sleep disturbances.

Cognitive dysfunction is one of the most common and consequential symptoms of MS. Impairments in processing speed, working memory, learning, executive function, visual-spatial processing, and language function affect 42-70% of MS patients, and constitute a major cause of loss of employment, caregiver stress, and reduced quality of life.[1-5] Despite the high prevalence and consequences of cognitive dysfunction in MS, the identification of appropriate strategies to minimize its impact is hindered by a poor understanding of factors that influence its severity, or common medical comorbidities that may increase patients' vulnerability to its effects.

Obstructive sleep apnea (OSA) is a common disorder characterized by repeated episodes of upper airway obstruction during sleep. Growing evidence suggests that nocturnal hypoxia caused by OSA contributes to cognitive dysfunction in the general population,[6-10] and that treatment for OSA in the form of positive airway pressure (PAP) therapy may improve cognitive dysfunction in individuals who do not have MS.[11, 12] Yet, the relationship between cognition and sleep apnea remains virtually unstudied in patients with MS. This is a critical gap in knowledge, as our recent data suggest that at least one fifth of MS patients carry a diagnosis of OSA, while a substantially higher proportion of patients (more than half) may have undiagnosed OSA. Furthermore, new data from our group suggest that OSA severity is closely related to reductions in cognitive performance in MS subjects.[13] These preliminary findings indicate that OSA could contribute to domains of cognitive dysfunction that are key aspects of morbidity in MS. Larger, prospective studies are now needed to demonstrate the nature and directionality of the relationship between sleep disordered breathing and cognitive dysfunction in individuals with MS. If a causal role does exist, identification and treatment of OSA could provide new opportunities improve cognition in persons with MS.

Objectives, Aims, and Endpoints

The objectives of this randomized, rater-blinded clinical trial are to 1) determine the effects of OSA on specific domains of cognitive function in patients with MS; and 2) assess the effects of OSA treatment with positive airway pressure (PAP) therapy on cognitive dysfunction in MS patients.

For Aim 1, subjects with MS (n~175) who screen positive on a commonly used screening tool for OSA (STOP-Bang questionnaire)[14] or who have a preexisting diagnosis of OSA but are not yet using PAP compliantly will undergo baseline cognitive testing and standard nocturnal polysomnography (PSG). For subjects who have a recent diagnosis of OSA based on recent (within 1 year) in-lab clinical University of Michigan Sleep Laboratory PSG who have not yet started using PAP treatment compliantly, their in-lab clinical PSG data will be used for baseline

analyses. After adjustment for clinical confounds and other PSG outcomes, we will assess the extent to which apnea severity as reflected by baseline PSG contributes to cognitive dysfunction in MS.

For Aim 2, subjects who meet criteria for OSA on baseline PSG or recent U-M Sleep Lab in-lab clinical PSG (n~140) will be randomized into one of 2 groups: expedited positive airway pressure (PAP) therapy, followed by repeat cognitive testing at 3 months post-PAP (Group 1, n~93), or standard care PAP therapy which will commence following completion of month 3 testing (Group 2, n~47). Mean changes from baseline in cognitive test scores will be compared between groups.

Assessments

The aims of this study are to assess the relationship between sleep apnea severity and cognitive dysfunction in MS patients with OSA (Aim 1), and to examine the effects of positive airway pressure (PAP) on cognitive function in MS patients with OSA (Aim 2).

N~175 patients who screen positive for high OSA risk on a validated screening questionnaire (STOP-Bang), or who already carry a diagnosis of OSA but are not yet using PAP on a compliant basis will be invited to participate.

Consenting subjects with STOP-Bang scores positive for >=2 risk factors for sleep apnea who are at high risk for OSA but who do not yet have a University of Michigan Sleep Laboratory PSG will undergo baseline (month 0) in-lab PSG and baseline neuropsychological (cognitive) testing. Subjects who have a recent diagnosis of OSA based on recent (within 1 year) in-lab clinical University of Michigan Sleep Laboratory PSG who have not yet started using PAP treatment compliantly will undergo baseline cognitive testing and their in-lab clinical PSG data will be used for baseline analyses. Subjects who have a diagnosis of OSA based on non-UM in-lab PSG or PSG > 1 year prior to screening will undergo new baseline PSG and baseline cognitive testing.

Subjects who meet criteria for OSA on baseline or clinical PSG (n~140, anticipated) will then be randomized into one of 2 groups (2:1 randomization): immediate treatment with PAP (Group 1, n~93) followed by repeat neuropsychological testing at 3 months post-PAP; or standard of care application of PAP at 3 months, after completion of repeat neuropsychological testing (Group 2, n~47). Analyses will focus on relationships between standard PSG measures (including the Respiratory Disturbance Index, oxygen desaturation index, and minimum oxygen saturation), innovative new quantitative PSG measures and cognitive test scores, as well as mean changes from baseline in individual and composite cognitive test scores following treatment with PAP therapy.

Statistical Methods

Analyses will focus on relationships between standard PSG measures (Respiratory Disturbance Index, oxygen desaturation index, and minimum oxygen saturation), innovative new quantitative PSG measures and cognitive test scores, as well as mean changes from baseline in individual cognitive scores following treatment with PAP therapy.

For aim 1, multivariate linear regression models will be used to analyze the effects of PSG-derived standard measures of sleep disordered breathing (including RDI, ODI, minimum O2 saturation), on individual cognitive test scores (continuous outcome variables of interest, in separate models). For Aim 2, multivariate linear regression models will be used to test the effects of Group effect on 3-month ("post") cognitive test scores, controlling for baseline ("pre") test scores and other covariates. We will also examine the association of PAP use as a continuous variable, based on mean nightly hours of use per month, on 3-month individual cognitive test scores, controlling for baseline scores.

1. INTRODUCTION

1.1 Indication

The proposed study will assess the relationship between obstructive sleep apnea severity and cognitive dysfunction in MS patients with OSA (Aim 1), and examine the effects of positive airway pressure (PAP) on cognitive function in MS patients with OSA (Aim 2).

1.2 Background and Rationale

Cognitive dysfunction is one of the most common and disabling consequences of multiple sclerosis.

Multiple sclerosis (MS) is a chronic, autoimmune disease that causes inflammation and destruction of the brain and spinal cord. In addition to physical disability, MS patients suffer disproportionately from a variety of complications that negatively impact quality of life, including cognitive dysfunction.

Cognitive dysfunction is one of the most consequential symptoms of MS, spanning multiple domains of function including processing speed, working memory, learning, executive function, visual-spatial processing, and language function. It is experienced by 42-70% of MS patients and is a major cause of loss of employment, caregiver stress, and reduced quality of life.[1-5] Compared to individuals with MS who report only physical impairments, those with cognitive impairments are more likely to be unemployed and suffer from a mental illness, less likely to engage in social or vocational activities, and have more difficulty carrying out some activities of daily living. Even individuals with MS who are not considered to be "cognitively impaired" per se, and those whose functioning may remain in the normal range, may experience mild to moderate declines in cognitive functioning which could contribute to distress and functional impairments. Despite its impact, there are no definitive treatments for cognitive dysfunction in MS. While cognitive rehabilitation in MS may help to enhance information processing and general level of function, this approach is still considered relatively new, and its utility remains under investigation. Adjunctive treatments aimed at improving cognitive functioning are sorely needed. Furthermore, the identification of appropriate strategies to prevent and remediate cognitive dysfunction in MS is hindered by a poor understanding of clinical features that may influence its severity, or comorbidities that may increase patients' vulnerability to its effects. *Further efforts are needed to identify and address clinical factors that could cause or exacerbate cognitive dysfunction in MS, and to identify patients who are most vulnerable to these effects*.

Obstructive sleep apnea (OSA) is a common and consequential medical disorder that causes cognitive dysfunction in the general population.

Obstructive sleep apnea (OSA) is a common disorder of sleep and breathing. The condition is characterized by repeated episodes of upper airway obstruction, hypoxia, and arousal during sleep. This growing epidemic is estimated to affect 10-20% of Americans, and is a well-recognized risk factor for many serious health consequences including hypertension, stroke, heart disease, and diabetes.[15, 16] Obstructive sleep apnea also carries a profound societal impact in the form of daytime sleepiness, lost productivity, and absenteeism in the workplace.[17, 18] The first-line treatment for OSA, Positive Airway Pressure (PAP), which is delivered by a mechanical device and mask interface, splints the upper airway open during sleep and effectively

ameliorates many of the symptoms caused by OSA. This air pressure can be continuous (CPAP), bi-level (BiPAP), or auto-adjusting (AutoPAP).

Obstructive sleep apnea is also an established cause of cognitive dysfunction in the general population.[6-9, 11, 12 10] Sustained intermittent hypoxia that arises from OSA in non-MS patients has been linked to myelin and axonal injury, gray matter atrophy, as well as impaired executive function, long-term visual and verbal memory, visuospatial/constructional abilities, and attention.[11, 19, 20 21, 22] Furthermore, treatment of OSA with PAP therapy has been shown to improve executive dysfunction, delayed long-term verbal and visual memory, attention/vigilance, global cognitive functioning, and gray matter volume in OSA patients without MS, *but the effect of OSA and its treatment with PAP therapy has not been studied in the context of comorbid MS.*

Clinical Rationale

Whereas the detrimental effects of OSA on cognition are well-established in the general population, the relationship between OSA and cognition has been virtually unstudied in patients with MS - a population that is particularly vulnerable to myelin and axonal damage by virtue of their neurological condition. This is a clinically relevant intersection, as MS is associated with a disproportionately high prevalence of OSA: new data from a recent study at our clinics show that at least 20% of MS patients suffer from clinically definite OSA, and up to 56% are at risk for OSA based on a validated screening tool (STOP-Bang).[23, 24]

Furthermore, preliminary findings from the investigators suggest that sleep disturbances, and OSA in particular, could contribute to domains of cognitive dysfunction that are key aspects of morbidity in MS. If a causal role does exist, identification and treatment of OSA could provide new opportunities to improve cognition in MS patients. **This study will for the first time prospectively evaluate the effects of OSA severity and its treatment on multiple key domains of cognitive function most affected in patients with MS, while controlling for other sleep- and MS-related variables that may influence these relationships.**

Hypotheses

Hypothesis 1: Sleep apnea severity, as reflected by standard PSG measures [respiratory disturbance index (RDI), oxygen desaturation index (ODI), and minimum oxygen saturation (Min O2)], as well as innovative new quantitative approaches, will be associated with reduced MACFIMS scores.

Hypothesis 2: Group 1, in comparison to Group 2, will show greater improvement from baseline in MACFIMS scores, on repeat MACFIMS testing at month 3.

1.3 Safety

Risks

This study presents minimal potential risks to participants. There are no alternatives to these data collection procedures. Participants may choose to not participate in any part of this voluntary study. Potential risks include: Discomfort during completion of study questionnaires or

cognitive testing, and/or discomfort related to sleep studies or wearing PSG equipment. The study team will take all reasonable steps to minimize these risks.

Study Questionnaires: The questionnaire battery, which requires the participants to reflect upon and report on their physical and emotional symptoms may cause mild emotional distress. Baseline and follow up questionnaires are expected to take approximately 30 minutes on average; during this time, participants may experience physical pain, fatigue, or boredom. Participants will have the option to take breaks and may elect to complete the questionnaires on another day if they are too tired or distressed. In addition, the names and contact information of the study team will be noted on the consent form and participants can contact them if needed.

Cognitive Testing: Cognitive testing is expected to take the average participant approximately 90 minutes to complete. During that time, it is possible that the participant may experience discomfort in the form of fatigue, physical pain, or boredom. In addition, if the participant perceives that they are not performing well, they may feel frustrated or emotionally distressed. The examiner who administers the cognitive tests will monitor the participant for signs of discomfort and distress and, as needed, will offer breaks and/or encouragement in the form of normalizing any emotional distress. In the event that a participant becomes extremely physically or emotionally uncomfortable, he or she may elect to discontinue testing or continue the remainder of the testing on another day.

In-laboratory overnight Polysomnography (sleep study) and Positive Airway Pressure (PAP) titration: The baseline sleep study (PSG) should not be painful and generally has few complications. Sensors or electrodes are placed on the scalp, face, chest, limbs, and a finger. The equipment records brain activity, eye movements, chin muscle activity, heart rate and rhythm, blood pressure, and the amount of oxygen in your blood. Elastic belts are placed around the chest and belly to measure chest movements and the strength and duration of inhaled and exhaled breaths. Additional sensors will measure airflow at the nose and mouth. Wires attached to the sensors transmit the data to a computer in the next room. The wires are very thin and flexible. They are bundled together so they don't restrict movement, disrupt sleep, or cause other discomfort. The most common side effect is mild irritation where electrodes come in contact with the skin. It may also be stressful to sleep away from the comfort of the subject's normal sleep environment. Subjects may sleep poorly in the lab, and as a result feel sleepy on the day after the study. For this reason, subjects are encouraged to ask someone to drive them to the sleep laboratory and take them home on the next morning. Skin integrity is checked by the sleep technologists. If subjects have a skin reaction at the site of a sensor used to monitor sleep or heart rate, the technologist will move it to another site and use a different type of tape or glue. If subject's skin should become irritated at multiple sites or in any severe manner, the study will be stopped. Any skin irritation at sites where sensors were placed is expected to resolve after the study on its own, usually in hours or at most a day or two.

Unless already performed for clinical purposes at U-M Sleep lab within the past year, participants who are diagnosed with OSA on baseline PSG will then undergo PAP titrations* to determine the ideal PAP machine setting(s), and participants will be prescribed clinical CPAP or BiPAP machines by clinicians involved in the study or their clinical sleep provider.

PAP therapy is considered standard clinical care for OSA. It involves wearing an apparatus that includes a hose and a mask (that covers the nose, or nose and mouth), connected to a small machine that blows air into the airway during sleep. The degree of air pressure given depends on the subject's apnea severity, and the supplied air pressure can be continuous or change with the subject's breathing pattern. This in-laboratory PAP titration sleep test uses the same sensors and has the same complications as the baseline sleep study, but the subject will also wear a mask attached to a PAP machine during sleep for this test, so that the sleep technicians can determine which type of mask and airway pressure are most appropriate. Masks can be uncomfortable and create a feeling of claustrophobia. Air pressure may dry out nasal passages. Subjects will be encouraged to alert the staff in the sleep laboratory to any other concerns, discomfort, or complications that arise during the PSG or PAP titration. A doctor will always be on call for any unexpected health emergencies.

*In some cases, insurance carriers will not cover the cost of an in-laboratory PAP titration, and instead will recommend an "auto-adjusting" PAP machine (also known as AutoPAP, or APAP) so that patients diagnosed with OSA may begin PAP without requiring a PAP titration. AutoPAP differs from a CPAP in that it uses algorithms to sense subtle changes in the user's breathing and deliver only the amount of pressure necessary to keep the airway open. AutoPAP can be also set to a straight CPAP mode, if determined necessary by the sleep provider, therefore offering more flexibility than a CPAP or BiPAP machine. In cases where AutoPAP is recommended by the participant's insurance carrier and no medical or PSG contraindications to AutoPAP exist, participants will be allowed to waive their in-lab PAP titration and start AutoPAP therapy according to their PAP randomization assignment.

PAP Therapy**:** There may be skin irritation related to the **PAP** mask, and masks can be uncomfortable and create a feeling of claustrophobia. There are multiple choices and sizes for sleep masks, and the provider will work with the subjects to find the most comfortable mask. There may be difficulty tolerating the forced air, but the pressure settings can be adjusted by working with the sleep machine provider. Subjects might experience a dry stuffy nose which can be treated with a saline nasal spray or humidified air that can be run through the PAP machine. The providers of these machines are very familiar with resolutions to and they will try and assist subjects in order to resolve any issues.

Confidentiality: The records of this study will remain confidential and protected; however, there is a risk for a breach of confidentiality. This risk is minimal, because a number of precautions have been taken in order to protect confidentiality. All data collected will be kept secure and in a locked office. Records will be coded and identifying information (such as name and registration numbers) will be removed and stored on a key in a separate location so that confidential information cannot be traced back to the subject. Only authorized members of the research team will have access to study records.

Standard care PAP treatment arm (for Group 2): Given that most consequences of OSA take months to years to manifest (cardiovascular disease, metabolic syndrome), we do not anticipate any significant long-term side effects from deferring PAP for 3 months for Group 2. Identification of sleep disordered breathing will be facilitated by enrollment into this study. Nonetheless, to avoid hazardous short-term consequences of OSA caused by excessive

sleepiness (e.g., motor vehicle accidents), ESS scores >= 16 on baseline or follow-up visits will be cause for study exclusion/discontinuation. This cutoff was chosen based on data that demonstrate an ordinal increase in risk of sleepy driving accidents with increases in ESS score, particularly in subjects with ESS scores > 15. We will also consider extreme OSA (RDI>60 respiratory events per hour, or unstable ECG rhythms on PSG) to be exclusionary, regardless of ESS score. For subjects who are not considered to be high risk per these criteria, we do not expect the risk of participating in this trial and having no CPAP for 3 months to exceed the risk encountered in routine clinical practice, as wait times for sleep clinic evaluations, subsequent sleep clinic referral, PSG, CPAP titration, and CPAP initiation at home currently often amount to 3 months or longer at U-M sleep clinics.

Alternative treatments and procedures: This study does not include an intervention. Therefore, there are no applicable alternative treatments or procedures.

As with any research study, there may be additional risks that are unforeseeable.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The objectives of this randomized, rater-blinded clinical trial are to 1) determine the effects of OSA on specific domains of cognitive function in patients with MS; and 2) assess the effects of OSA treatment with positive airway pressure (PAP) therapy on cognitive dysfunction in MS patients.

2.2 Endpoints

2.2.1 Primary Endpoint(s)

Effects of PSG-derived standard measures of sleep disordered breathing (including RDI, ODI, minimum O2 saturation), on cognitive test scores.

Effects of PAP therapy on cognition, as measured by mean change from baseline in cognitive test scores in Group 1 (expedited PAP therapy) compared to Group 2 (delayed PAP therapy).

2.2.2 ExploratoryEndpoints

Effects of standard and novel PSG-derived measures of sleep disturbances (including TST, WASO, TAI, SE, RCREC, and sleep stage dynamics) on cognitive test scores.

Mean change from baseline in subjective sleepiness, as measured by the Epworth Sleepiness Scale, in group 1 vs group 2;

Mean change from baseline in daytime fatigue level, as measured by the Fatigue Severity Scale, in group 1 vs group 2;

Mean change from baseline in insomnia level, as measured by the Insomnia Severity Index, in group 1 vs group 2;

Mean change from baseline in quality of life and chronic daily symptoms (fatigue, anxiety, pain) as assessed by the Patient Reported Outcomes Measurement Information System (PROMIS, www.nihpromis.org/), in group 1 vs group 2.

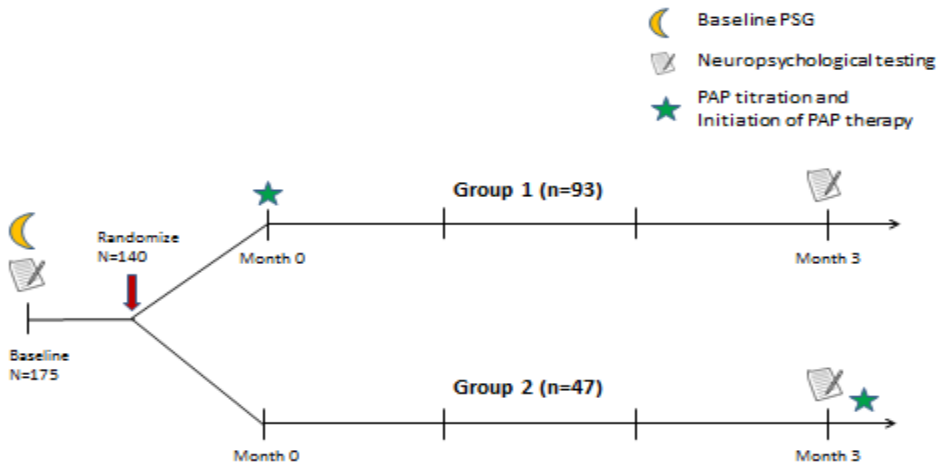
3. STUDY DESIGN

N~175 patients who screen positive for high OSA risk on a validated screening questionnaire (STOP-Bang) given during routine MS Clinic appointments at the University of Michigan will be invited to participate. Additional subjects may be recruited from the community through a U-M electronic clinical trials registry (UMclinicalstudies.org); a clinicaltrials.gov posting; print or electronic newspaper advertisement; fliers at the medical center and in the community; and from study advertisements posted by the University of Michigan on Facebook and Twitter. Potential subjects who contact the study staff directly, or are referred by outside providers, and have not completed a STOP-Bang questionnaire, will be asked the STOP-Bang questions via telephone during a pre-screening interview. If their STOP-Bang assessment indicates a risk for sleep apnea (score >=2 risk factors for sleep apnea), they will be invited to participate. If their STOP-Bang score is below a 2, they will not be eligible for the study.

Subjects who endorse a pre-existing diagnosis of OSA who are not yet using PAP therapy on a compliant basis - but who express an interest to start using it - will also be invited to participate.

Consenting subjects with elevated STOP-Bang scores or those who are at high risk for OSA will undergo baseline (month 0) PSG and baseline neuropsychological testing (MACFIMS) (see figure). Subjects who already have recent U-M in-lab PSG (within 1 year) indicating OSA will also undergo baseline cognitive testing, and their in-lab clinical PSG data will be used for baseline analyses. Subjects who have a diagnosis of OSA based on non-UM lab PSG or PSG > 1 year prior to screening will undergo baseline PSG and baseline cognitive testing.

Subjects who meet criteria for OSA on baseline or clinical in-lab PSG (n~140, anticipated) will then be randomized into one of two groups (2:1 randomization): immediate treatment with PAP (Group 1, n~93) followed by repeat neuropsychological testing at 3 months post-PAP; or standard of care application of PAP at 3 months post-randomization, after completion of repeat neuropsychological testing (Group 2, n~47). Analyses will focus on relationships between standard PSG measures (Respiratory Disturbance Index, oxygen desaturation index, and minimum oxygen saturation), innovative new quantitative PSG measures and MACFIMS scores, as well as mean changes from baseline in individual and composite MACFIMS scores following treatment with PAP therapy.



4. SUBJECT SELECTION

4.0 Subject Recruitment

The projected number of subjects for enrollment is N~175, all diagnosed with clinically definite MS. Subjects will be recruited from the University of Michigan (U-M) MS Clinic during routine appointments. An additional recruitment site will include a new, first-of-its-kind Sleep and MS Multidisciplinary Clinic, founded by the investigators (Drs. Braley and Chervin). Additional subjects may be recruited from the community through a U-M electronic clinical trials registry (UMclinicalstudies.org); a clinicaltrials.gov posting; print or electronic newspaper advertisement; fliers at the medical center and in the community; and from study advertisements posted by the University of Michigan on Facebook and Twitter. Information on the study will also be available via letter to medical colleagues in the community, advertised on a posted flyer, advertised via the internet through the UM research recruiting website (https://umclinicalstudies.org), advertised on a registry of clinical trials run by the United States National Library of Medicine (NLM) at the National Institutes of Health (clincicaltrials.gov), and advertised on Craigslist.

4.1 Inclusion Criteria

1) Age of 18-70 years at screening
2) Diagnosis of clinically definite MS
3) Willingness to undergo in-lab baseline polysomnography (PSG) and positive airway pressure (PAP) titration (if needed)
4) Willingness to undergo 2 separate 90-minute cognitive testing sessions
5) Either one of the following:

   Score of >=2 sleep apnea risk factors on the "STOP-Bang" sleep apnea screening questionnaire. The STOP-Bang questionnaire is a screening tool consisting of eight items which reflect OSA risk factors. STOP-Bang scores of ≥3 indicate elevated risk for moderate-severe OSA in the general population, and scores as low as 2 are frequently seen in MS patients with OSA, based on previous data from the PI).

OR

Have a pre-existing diagnosis of OSA based on a previous overnight sleep study (either home study or in-lab) but have not yet started using PAP therapy on a compliant basis. *If OSA was NOT diagnosed by a U-M in-lab sleep study within the past year prior to screening, subjects must be willing to get new baseline in-lab U-M PSG as part of study.

6) Willingness to start treatment with PAP if OSA present

4.2 Exclusion Criteria

1) Physical, psychiatric or cognitive impairment that prevents informed consent, PSG, PAP use, or reliable longitudinal follow-up
2) Cardiopulmonary conditions that may increase sleep apnea risk
3) Current treatment, such as PAP, for obstructive or central sleep apnea
4) History of surgical treatment for OSA
5) Nervous system diseases other than MS that may predispose subjects to OSA (such as Parkinson's disease, amyotrophic lateral sclerosis, or recent stroke)
6) History of concomitant central nervous system disease that could influence cognition, such as large vessel territory stroke, Alzheimer's disease, Parkinson's disease, or Lewy body dementia
7) Concomitant systemic autoimmune disease with secondary central nervous system involvement (including CNS lupus or neurosarcoidosis).
8) Pregnancy
9) Evidence of clinical MS relapse within the last 30 days prior to enrollment
10) Systemic high dose steroid use (1 gram IV methylprednisolone daily for 3-5 days or equivalent)for an MS relapse within the last 30 days prior to enrollment
11) Unwillingness to initiate PAP therapy if clinically indicated
12) Severe depression at screening per the Patient Health Questionnaire-8 (PHQ-8) (The PHQ-8 is a brief, self-administered questionnaire that evaluates core symptoms associated with major depressive disorder. Scores range from 0 to 24 based on the frequency and severity of depressive symptoms over the previous two weeks.)
13) Anticipated initiation, dosage change, or discontinuation in medications that could, per the opinion of the investigators, influence cognitive test scores from baseline to follow-up, including MS disease modifying therapies, hypnotic agents, narcotic-based medications, benzodiazepines, antispasmodics, or 4-aminopyridine
14) ESS scores >= 16 on baseline visit
15) Subjects with extreme OSA accompanied by signs of cardiopulmonary compromise (RDI>60 respiratory events per hour with severe nocturnal hypoxia or unstable ECG rhythms on PSG), will be excluded unless they are randomized to immediate PAP arm
16) Any other condition or treatment that in the opinion of the investigator could affect subject safety or study eligibility

Table 1: STOP-Bang questionnaire	
Snoring	Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?
Tired	Do you often feel tired, fatigued, or sleepy during the daytime?
Observed Apneas	Has anyone ever observed you stop breathing during your sleep?
Blood **P**ressure	Do you have or are you being treated for high blood pressure?
BMI	BMI more than 35 kg/m2?
Age	Age over 50 years old?
Neck circumference	Are you a male with a neck circumference greater than 17 inches, or a female with a neck circumference greater than 16 inches?
Gender	Are you a male?

5. STUDY TREATMENTS

5.1 Allocation to Treatment (see also 6.4)

Randomization Process: Subjects who meet all Inclusion/Exclusion criteria, including OSA on baseline or clinical PSG, will be randomized (2:1 randomization) to expedited PAP therapy (Group 1, n~93), or standard care PAP therapy (Group 2, n~47), after the subject has signed consent, completed the baseline activities, Randomization will be stratified by sleep apnea severity (RDI < or >=30) to minimize imbalances in apnea severity between groups.

5.2 Blinding

PSG technicians, PSG interpreters, and study staff who conduct and score neuropsychological tests will remain blinded to group allocation for the duration of the study. **The subject, PI, co-investigators, coordinators, and statistician will not be blinded.**

5.3 Treatment with Positive Airway Pressure (PAP) Therapy: Unless already performed at U-M sleep lab within the past year, all subjects who are diagnosed with OSA on baseline or clinical PSG (n~140) will undergo PAP titrations* and be prescribed clinical PAP therapy by clinicians involved in the study or the subject's treating sleep provider. PAP therapy is considered standard clinical care for patients with obstructive sleep apnea. PAP is a mode of respiratory ventilation that blows air into the nose (or nose and mouth) to splint the upper airway open during sleep. PAP therapy can be delivered at a continuous pressure (CPAP), at different levels during inspiration and expiration (BiPAP), or at a range of auto-adjustable levels depending on the patient's breathing (AutoPAP)*. In order to determine which pressure setting most effectively treats an individual's sleep apnea, an overnight PAP titration study is typically required. This study is similar to a PSG in terms of overnight monitoring but also involves fitting of various masks which are then hooked up to the subject and PAP machine to test the effectiveness of various PAP settings, and to determine which mask/setting is most tolerable for the subject. PAP titration studies will be scored by certified PSG technologists and interpreted by a board-certified sleep physician, who will then place an order for PAP equipment at appropriate settings with a local durable medical equipment (DME) provider. DME will be covered by the subject's insurance.

* In some cases, insurance carriers will not cover the cost of an in-laboratory PAP titration, and instead will recommend an "auto-adjusting" PAP machine (also known as AutoPAP, or APAP) so that patients diagnosed with OSA may begin PAP without requiring a PAP titration. AutoPAP differs from a CPAP in that it uses algorithms to sense subtle changes in the user's breathing and deliver only the amount of pressure necessary to keep the airway open. In cases where AutoPAP is recommended by the participant's insurance carrier and no medical or PSG contraindications to AutoPAP exist, participants will be allowed to waive their in-lab PAP titration and start AutoPAP therapy according to their PAP randomization assignment.

6. STUDY PROCEDURES

6.1 Screening/Baseline Visit

Subjects will be seen at one of several University of Michigan clinical or research study sites for baseline visit activities, including but not limited to the Michigan Clinical Research Unit (MCRU), or the Department of Neuropsychology testing suite in the Med-Inn Building. Inclusion and Exclusion Criteria will be reviewed, and informed consent will be obtained by qualified study staff. Consenting subjects who meet eligibility criteria at screening will be enrolled and receive their baseline evaluation, where they will undergo the following assessments:

1) Demographic information
2) Focused medical and surgical history as it relates to multiple sclerosis, sleep, and cardiopulmonary history
3) Medication review
4) Assessments of height, weight, and neck circumference
5) Expanded Disability Status Scale self-report questionnaire (a self-reported measure of MS-related disability)
6) Pregnancy test (for females of childbearing age)
   (if a pregnancy test was performed within the past month, that result may be used and the test does not need to be repeated)
7) Fatigue, insomnia, and sleepiness assessments (see 7.2)
8) Pain, anxiety, and quality of life assessments (see 7.2)
9) Baseline neuropsychological testing (see 6.2)*
10) Unless already done clinically at U-M sleep lab within the past year, baseline polysomnography (PSG, see 6.3)

*If subjects are unable to complete baseline neuropsychological testing on the day of their baseline visit, this will be scheduled within 3 weeks of screening/baseline visit.

6.2 Cognitive (Neuropsychological) Testing

The Minimal Assessment of Cognitive Function in MS (MACFIMS)[26, 27] is a validated, 90-minute neuropsychological battery comprised of a collection of standardized cognitive tests

which assess 5 main cognitive domains that are commonly affected in MS: processing speed/working memory, learning, executive function, visual-spatial processing, and language function, using 7 standard measures. Endorsed by the Consortium of Multiple Sclerosis Specialists (CMSC), it is one of the most accepted neuropsychological batteries in the field. All MACFIMS testing will be performed by blinded, trained psychometricians who are part of the pool of technicians in the department of Psychiatry at the University of Michigan. All psychometricians are directly supervised by an onsite Ph.D.-level neuropsychologist in Psychiatry; furthermore, Dr. Kratz, a clinical psychologist who is a co-investigator on this project will oversee all neuropsychological data collection and extraction. Components of the MACFIMS, include in this study are as follows:

Symbol Digit Modalities Test (SDMT): Consists of a series of 9 symbols paired with a single digit in a key at the top of an exam sheet. Below the key, the remainder of the page consists of pseudo-randomized sequence of these symbols, and the examinee must recall the correct corresponding digit as quickly as possible, either by scanning the key, or using recall. The final score consists of the total number of items correct within a 90 second testing interval. The **oral administration** will be used for this study. The Standard Form and Alternate Form of the SDMT will be used.

Paced auditory serial addition test (PASAT): Patients listen to a series of audiotaped digits and must add each consecutive digit to the one immediately preceding it. Digits presented at two different rates (every 2 seconds or 3 seconds). Scores reflect the total number of correct responses at each presentation rate (PASAT-2 or PASAT-3). Two alternate forms, Form A and Form B, will used in this study.

California Verbal Learning Test (CVLT-II): Subjects learn a 16-word list (list A), the recall of which is examined over a course of 5 trials. Subjects are then asked to recall a new 16-word list (interference list, List B), after which time the original list is reassessed after a 25-minute delay interval. Total number of words recalled on trials 1-5 and delayed recall are scored. The CVLT-II has both a Standard Form and an Alternative form that will be used in this study.

Brief Visuospatial Memory Test – Revised (BVMT-R): Assesses spatial learning and memory using a matrix of simple abstract designs presented in three trials (10 seconds each). Subjects are asked to recall (immediate and after a delay) and recognize the designs from distractor designs. Form 1 and Form 2 will be used in this trial.

Judgment of line orientation test (JLO): Measure of visual-spatial abilities. Subjects are required to identify the angle defined by 2 stimulus lines, from those which are located in a visual array of lines that cover 180 degrees. Scores reflect total number of correct responses. Form H and a Form V will be used in this study.

Controlled word association test (COWAT): Measure of phonemic fluency, in which subjects are asked to name as many words as they can that begin with 3 different stimulus letters within 60 seconds. Scores reflect total number of words generated across all 3 trials. Two alternate versions (CFL/PRW) of the COWAT will be used.

Nine-hole Peg Test (NHPT): Using a standard NHPT board, subjects place plastic pegs into 9 holes one at a time, and remove them one at a time as quickly as they can. Test is scored as

the time (seconds) it takes the subject to complete the task. Two trials on both dominate and non-dominate hands are completed.

Trail Making Test (Part A and B): Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

The North American Adult Reading Test (NAART) - 35: The NAART is a widely used to estimate verbal intellectual ability/verbal intelligence. The test consists of a list of 35 irregularly pronounced English words. The examinee is required to read each word, and their score is based on the number of correctly pronounced words (according to American and Canadian punctuation rules). Because scores on the NAART are thought to reflect basic aspects of crystalized intelligence and are not expected to change, this test will only be administered once – at baseline.

Go/No-go test: The GNG task involves the presentation of letter stimuli one at a time every 500 ms on the computer screen. After a brief training session, participants are instructed to quickly press a button each time they see the target letters X, Y or Z: either 1) each time the target letters are presented (go trials), or only when the target letters are presented in alternating non-repeating fashion (no-go trials). Reaction time and accuracy are recorded.

Two fixed batteries of these tests (see **table 2** below) will be created. Order of administration of Fixed Test Battery A and Fixed Test Battery B will be randomized across subjects.

Table 2: Cognitive batteries		
Test	**Fixed Test Battery A**	**Fixed Test Battery B**
SDMT	Standard Form	Alternate Form
PASAT 3	Form A	Form B
PASAT 2	Form A	Form B
CVLT-II	Standard Form	Alternate Form
BVMT-R	Form 1	Form 2
JLO	Form H	Form V
COWAT	CFL	PRW
NHPT	Standard administration	Standard Administration
Trails A and B	Standard form	Alternative form
NAART	Standard Form – baseline only	Standard form – baseline only
Go/No-go test	Standard administration	Standard administration

6.3 Baseline PSG visit*

Conventional In-lab Overnight Polysomnography (PSG): Procedures and scoring will follow the latest American Academy of Sleep Medicine Scoring Rules.[28] Standard measures will include: total sleep time (TST), sleep efficiency, sleep latency (SL [minutes from lights out to first 30 seconds of any sleep stage]), wake after sleep onset, total arousal index (TAI, average number of EEG arousals per hour of sleep), % total sleep time spent in stage 1, 2, 3, and REM sleep, the Respiratory Disturbance Index (RDI - total number of apneas, hypopneas and respiratory-related arousals per hour of sleep)central apnea index (total number of central apneas per hour of sleep), oxygen desaturation index (ODI, number of desaturation events >=3% below baseline oxygen saturation levels), minimum oxygen saturation (Min O2), and % of sleep time with O2 saturation ≤ 88%. PSG's will be scored by a single, experienced, technologist, masked to treatment group. Scoring will be reviewed and confirmed, and studies interpreted, by a board-certified sleep specialist.

Innovative PSG Signal Analysis Algorithms: In addition to conventional PSG measures, PSG data will also be analyzed using a novel PSG algorithm that has never been applied to sleep or cognitive research in MS patients. **This will involve no changes to the subject's overnight PSG procedure or experience**. This novel method, invented and patented by co-investigators Drs. Chervin and Burns,[29, 30] uses variations in EEG power (for specific frequency bands) during discrete phases of the respiratory cycle (early expiration, late expiration, early inspiration, and late inspiration) to detect subtle, cortical microarousals not visible on standard visual inspection of the PSG.28-30 This algorithm will allow a more sensitive evaluation of potential effects that disordered nocturnal respiration could have on cerebral cortical function among MS patients. Specifically, respiratory cycle-related EEG changes (RCREC), which reflect cortical microarousals, will be computed to detect subtle disturbances in respiration beyond standard apnea/hypopnea measures, which will then be correlated with MACFIMS scores.

The study team has also pioneered the application of analyses of sleep dynamics – temporal patterns of sleep stages rather than simpler total sums or percentages of stage 1, 2, 3, and REM sleep – to discriminate between disordered and normal sleep when standard measures fail to do so. These techniques also will be applied to sleep recordings, to identify additional sleep-related predictors of cognitive dysfunction beyond conventional measures of nocturnal respiration in MS patients.

*For subjects who have a recent diagnosis of OSA based on recent (within 1 year) clinical University of Michigan Sleep Laboratory PSG, these clinical PSG data will be used for the same baseline analyses above.

6.4 Randomization

Randomization Process/Blinding: Subjects who meet criteria for OSA on baseline or clinical PSG (n~140, anticipated) will be randomized (2:1 randomization) to determine whether they will receive expedited PAP therapy (Group 1, n~93), or standard of care PAP therapy (Group 2, n~47). Computer-based randomization will be stratified by sleep apnea severity (RDI < or >=30) to minimize imbalances in apnea severity between groups. PSG technicians, PSG interpreters, and study staff who conduct and score neuropsychological tests will remain blinded to group allocation for the duration of the study. The subject, PI, co-investigators, coordinators, and statistician will not be blinded. **Subjects will be contacted with the randomization**

assignment that determines whether they will be scheduled for immediate PAP titration (Group 1) or delayed PAP titration after their month 3 cognitive testing.

6.5 PAP titration
(After randomization for Group 1, and following month 3 cognitive testing for Group 2)

Standard AASM guidelines will be followed in laboratory-based PAP titration studies designed to determine effective continuous PAP (CPAP) or bilevel PAP (BiPAP) settings, when necessary, for subjects with OSA. Studies will be scored by certified PSG technologists and interpreted by a board-certified sleep physician. Clinicians involved in the study or the subject's treating sleep provider will then place an order for PAP equipment at appropriate settings with a local durable medical equipment (DME) provider. DME will be covered by the subject's insurance. The DME company will provide subjects with equipment, instruct them on proper use at home, and provide supplies as needed. PAP titrations can be waived if subjects have had a recent U-M sleep lab clinical PAP titration within the past year. In cases where AutoPAP is recommended by the participant's insurance carrier and no medical or PSG contraindications to AutoPAP exist, participants will be allowed to waive their in-lab PAP titration and start AutoPAP therapy according to their PAP randomization assignment. Adherence of PAP therapy will be monitored by electronic downloads or datacards within the PAP machines.

6.6 Month 1 and Month 2 Follow-up Visits/Assessments

Group 1: 1 and 2 months following <u>PAP initiation</u> – *Group 1 subjects will have the option of doing their MONTH 2 assessment by phone or in person*

Group 2: 1 and 2 months following <u>randomization</u> – *Group 2 subjects will have the option of doing either of these assessments by phone or in person*

All randomized subjects will undergo the following assessments:

1) Focused medical and surgical history as it relates to MS, sleep, and cardiopulmonary history
2) Medication review
3) PAP compliance review (datacard assessment) for Group 1
4) Fatigue, insomnia, and sleepiness assessments (see 7.2)
5) AE/SAE review

6.7 Month 3 Visit with repeat Cognitive Testing

Group 1: 3 months after <u>PAP initiation</u>
Group 2: 3 months after <u>randomization</u>

All randomized subjects will undergo the following assessments:

1) Focused medical and surgical history as it relates to MS, sleep, and cardiopulmonary history
2) Medication review
3) PAP compliance review for Group 1
4) Fatigue, insomnia, and sleepiness assessments (see 7.2)

5) Pain, anxiety, and quality of life assessments (see 7.2)
6) AE/SAE review
7) Repeat neuropsychological testing (see 6.2)
8) PAP titration for group 2 (if applicable)*

* Group 2 subjects are encouraged to undergo PAP titration on the night of the Month 3 visit. If they agree to this approach, the PAP titration will be scheduled around the time of the Month 2 visit.

6.8 Post-Study Follow-up phone assessment for Group 2 (1 month after Month 3 visit)

Following the Month 3 visit (and once the PAP titration is complete) , for Group 2 subjects who still express a desire to proceed with PAP treatment, the study team will contact the subject and/or DME company (phone or email) to confirm that a PAP prescription has been faxed to the subject's designated DME company), and if applicable, that UM sleep clinic follow up has been made. Three phone contacts will be attempted. Any barriers to the PAP prescription process will be passed on to sleep clinic staff for appropriate action. If no clinic follow up has been scheduled per the subject's account (and the subject still desires a sleep clinic appointment), the study team will contact appropriate UM sleep clinic personnel to contact the subject.

SCHEDULE OF ACTIVITIES

Study Activity	Baseline Visit	Baseline PSG visit	Month 0	Month 1	Month 2	Month 3
Demographics	X					
Medical/Surgical History	X			X	X	X
Medication review	X			X	X	X
Height, weight, neck circumference	X					
EDSS self-report	X					
AE/SAE review	X			X	X	X
Baseline neuropsych testing (all subjects)	X					
Repeat neuropsychological testing (OSA subjects)						X
Baseline PSG (all subjects who do not have U-M PSG within the past year)		X				
Randomization (for subjects with OSA on baseline PSG)			X			
PAP titration/prescription for Group 1			X			
PAP compliance review for Group 1				X	X	X
Fatigue (FSS), insomnia (ISI), and sleepiness (ESS) surveys	X			X	X	X
PROMIS/NeuroQOL measures	X					X

7. ASSESSMENTS

7.1 Primary Endpoint Assessments

Cognitive performance (primary outcome measure of interest) will be assessed with formal neuropsychological testing (see section 6.2). Sleep apnea severity (primary predictor of interest) will be assessed with overnight polysomnography (see section 6.3).

7.2 Exploratory

Measures of sleep quality and sleep fragmentation, as well as Innovative PSG Signal Analysis Algorithms (secondary predictors of cognitive performance), will be assessed with overnight polysomnography (see section 6.3).

Epworth Sleepiness Scale (ESS): The ESS is an 8-item questionnaire that asks about the likelihood of dozing in variably sedentary situations.[31] This commonly used measure of subjective sleepiness, or sleep propensity, is reliable, internally consistent, and validated against objective polysomnographic measures. A score ≥10 suggests excessive sleepiness.

Krupp's Fatigue Severity Scale (FSS): The FSS is a validated, 9-item instrument that measures the impact of fatigue on multiple outcomes, with a physical focus.[32] Prior studies have shown acceptable internal consistency and stability over time, and sensitivity to change that correlates with the subject's clinical improvement. Many if not most past studies on MS-related fatigue have used the FSS.

Insomnia Severity Index (ISI): The Insomnia Severity Index (ISI) is a 7-item questionnaire with 5-point Likert scale responses designed to assess the nature, severity, and impact of insomnia in adults. [33] Scores of 15 or higher reflect moderate clinical insomnia.

Patient Reported Outcomes Measurement Information System (PROMIS)/Quality of Life in Neurological Disorders (NeuroQol): The federally-funded Patient Reported Outcomes Measurement Information System (PROMIS) and Quality of Life in Neurological Disorders (NeuroQoL) are two integrated systems of highly reliable and responsive assessment tools that use modern measurement theory to assess patient-reported health related quality of life. Using validated item banks and standardized metrics, PROMIS and NeuroQoL reliably measure patient-reported outcome measures (PROM's) for clinical research. PROMIS and NeuroQoL measures, derived from large question banks, can be given as static short forms (typically 7-8 items in length). Measures can be used as primary or secondary endpoints in clinical studies that assess treatment effect for multiple symptoms including quality of life, pain, anxiety, fatigue and sleep quality (www.nihpromis.org/; www.neruoqol.org).

7.2.1 General Medical History

General medical history will be assessed at baseline and in all follow-up visits. Subjects will be queried about any chronic or ongoing health conditions that require treatment (which will be recorded in the CRF). Subjects will also be asked to provide their list of medications and allergies.

7.2.2 Concomitant Medication Use

Concomitant medications will be assessed at each visit and/or phone contact and recorded in the CRF.

7.2.3 Adverse Events

Adverse events will be assessed at each visit by questioning subjects about any symptoms they have been experiencing while on the study.

8. ADVERSE EVENT REPORTING

Multiple Sclerosis is a disease with many disease-related symptoms and complications, and there are many common mild side effects associated with PAP therapy. Due to the patient population and the nature of the disease, as well as the lack of experimental interventions in this study (only standard of care procedures and treatments will be used) we would like to implement the following AE/SAE collection/reporting guidelines:

SAE events that meet all 3 of the following criteria will be collected and submitted:

- Serious;
- Related; and
- Unanticipated

In addition, the following AEs will be collected and submitted:

- Any AE that results in a change to research

9.0 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

Estimates (means and standard deviations) are derived from our recent data that evaluated SDMT scores among MS subjects referred for overnight PSG, and previously published interventional studies in that evaluated the effects of medical interventions on components of the MACFIMS in MS patients. We have chosen to focus on SDMT score as the primary outcome variable of interest, as the SDMT encompasses multiple domains of cognitive function, is frequently used in MS clinical studies as a reliable measure of cognitive impairment, and is sensitive to changes in intervention.

Based on a power analysis of two sample means (unequal sample sizes, with 2:1 randomization) with a 0.05 two-sided significance level, and an estimated S.D. of 9, a total sample size of 140 subjects will have an 86.3% power to detect a 5-point difference in SDMT score between groups, on month 3 testing, for hypothesis 2. Similarly, using individual MACFIMS components as outcome variables (in separate models), a multiple linear regression power analysis shows that a sample size of n=140 subjects will yield 88% power to detect an R-square difference of 0.05 for the test predictor of interest (% PAP use per month, as a continuous measure), assuming the R-squared explained by the adjustment variables is at least 0.3.

Although we predict a low dropout rate due to the short duration of the study, if we assume a dropout rate of 15% (10 dropouts per group), we will still have a power of 81.2% power to detect a 5-point difference in SDMT score between groups, on month 3 testing.

9.2 Analysis of Primary Endpoint

Aim 1: Multivariate linear regression models will be used to analyze the effects of baseline PSG-derived standard measures of sleep disordered breathing (including RDI, ODI, minimum O2 saturation), on individual cognitive test scores (continuous outcome variables of interest, in separate models) for Aim 1, controlling for other sleep, serological, and clinical variables. Additional models that use computed respiratory cycle-related EEG changes (calculated as the maximum difference between the mean EEG powers associated with each of the 4 respiratory cycle segments as predictor variables) will be used to evaluate the effects of respiratory-related cortical microarousals on cognitive test scores, controlling for other clinical and sleep-related variables. Separate models that use computed temporal patterns of sleep stages as predictors of cognitive test scores will also be constructed.

Aim 2: Multivariate linear regression models will be used to test the effects of Group effect on 3-month ("post") cognitive test scores, controlling for baseline ("pre") test scores. We will also examine the association of PAP use as a continuous variable, based on mean nightly hours of use per month, on 3-month individual cognitive test scores, controlling for baseline scores. Separate models will be used for each cognitive test of interest. Predictor variables that are unbalanced between groups despite randomization will be used as covariates in the analyses.

To evaluate early effects of PAP therapy on cognitive scores, sleep stage dynamics will also be assessed during PAP titrations to determine whether changes in sleep stage stability predict improvements on cognitive test scores in separate models.

9.3 Analysis of exploratory endpoints

Multiple linear regression models will be used to assess the effect of PAP treatment effect (Group 1 vs. Group 2 effect) on tertiary outcome measures including daytime sleepiness (ESS scores), fatigue (FSS, PROMIS scores), and anxiety, pain, and quality of life (PROMIS scores).

10. MONITORING

10.1 Data Safety Monitoring Plan

Monitoring of the study will be conducted by a qualified clinical trial monitor according to an established monitoring plan. All subjects who are diagnosed with OSA will also be overseen by a certified sleep provider throughout the duration of the study, who will then continue to follow them once study activities have ceased. Subjects who are not already established patients in the U-M MS/sleep clinic will be referred for expedited sleep clinic follow up following their PSG diagnosis of OSA. Whenever possible, these clinical visits will occur in tandem with study visits.

Although none of the measures in this study assess self-harm, in the event that a participant mentions suicidal ideation or other severe mental distress that could result in harm to self or others, Dr. Anna Kratz (Co-Investigator), who is a licensed psychologist, will contact the participant by phone and complete a standard self-harm/suicide assessment, taking appropriate action (e.g. referral for mental health services, contacting emergency services) as needed. All safety related incidents will be reported to the PI and the IRB according to relevant protocols.

10.2 Monitoring Plan and Information

To assure adequate protection of the rights of human subjects, per 21 CFR 312.50 and 312.53, the study will be monitored to ensure that the study is implemented in accordance with the protocol and applicable federal and local regulations, that proper informed consent procedures were followed and to insure the integrity and quality of the data.

A qualified trial monitor will be selected, per 21 CFR 312.53(d) to monitor the trial in accordance with the protocol and all applicable regulatory requirements. A monitoring plan will be established to ensure the quality and integrity of the data through pre-investigation, periodic site visits, review of adverse events/subject records, etc. The Michigan Institute for Clinical and Health Research (MICHR) will assist with the selection and support of the monitor assigned for this proposed clinical investigation and prepare the monitoring plan.

11. DATA HANDLING AND RECORD KEEPING

11.1 CRFs / Electronic Data Record

CRFs, in paper or electronic format, will be utilized and maintained by the study staff. Entries made in the CRF must be verifiable against source documents, unless the CRF is considered to be the source document.

11.2 Record Retention

Per 21 CRF §312.62, study records will be retained for a minimum of 7 years after the investigation is discontinued.

12. ETHICS

12.1 IRB

Prior to study commencement, the study will be reviewed and approved by the Institutional Review Board (IRBMED, University of Michigan, Ann Arbor, MI).

12.2 Subject Information and Consent

A study team member will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and will be submitted for IRB approval.

13. STUDY DISCONTINUATION CRITERIA

Stopping Rules for Safety Reasons

Subjects who demonstrate evidence of severe excessive daytime sleepiness (as evidenced by ESS scores >= 16 at baseline) will result in exclusion from study. Subjects with extreme OSA that is accompanied by signs of cardiopulmonary compromise or severe nocturnal hypoxia on baseline PSG will also result in study exclusion unless they are randomized to expedited PAP arm. In such cases, subjects will be referred for expedited sleep clinic follow-up.

Discontinuation of a Subject

In the event a patient drops out of the study or is discontinued due to protocol violations, all attempts will be made to exit the patient in accordance with the protocol requirements.

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