



## Strategic Research Grant *Guidelines for a Letter of Intent*

The AASM Foundation requests that prospective applicants submit a letter of intent (LOI) prior to submission of a grant application for the Strategic Research Grant. LOIs are competitive and reviewed by the AASM Foundation Executive Committee to ensure that the proposed research is responsive to the topic of interest listed in the Strategic Research Grant request for applications.

The LOI should be no more than three pages (excluding references). Figures and general tables are allowed and will be included in the three-page limit. The LOI must include the following:

### **A. Descriptive Title of Proposed Research**

### **B. Research Domain and Topic Responsiveness**

- *Explain how the proposed research is responsive to the research domain and topic listed in the RFA.*

### **C. Specific Aims**

- *State the goals of the proposed research, the comparators (if applicable), and the expected outcomes.*

### **D. Background**

- *Describe the evidence gap(s) by referencing systematic review(s), guidelines, and other previously published data.*

### **E. Significance**

- *Describe the potential for the study to advance the field of sleep medicine.*

### **F. Approach**

- *Describe the overall approach to be used to accomplish the specific aims.*
  - 1. Study Design:** *Briefly describe the study design.*
  - 2. Study Population and Setting:** *Specify the study population and the settings.*
  - 3. Comparators (if applicable):** *List the options compared and provide evidence of efficacy or wide use for these interventions.*
  - 4. Outcomes:** *Describe the outcomes representing the population of interest.*

### **G. Diversity, Equity, and Inclusion**

- *Describe how the planned research has considered diversity, equity, and inclusion in the proposed study population; alternately, provide any scientific or ethical reasons for limiting diversity, equity and inclusion in the proposed study population.*

### **H. Investigator and Key Personnel**



- *Provide the experience and expertise of the investigator(s) and key personnel needed to conduct the research.*

**I. References** *(not included in page limit)*

**Formatting Requirements:**

- **Header:** Include the Principal Investigator's full name on every page in the top-left corner
- **Font:** Times New Roman 11 pt or 12 pt font; figures, tables, and captions may have 8 pt font
- **Spacing:** Single
- **Margins:** No less than 0.50 inches. (The header may fall within the top margin, but the body text may not begin closer than a half-inch from the edge of the page.)
- **Page numbers:** Consecutive
- **Page limit:** Three pages (excluding references)
- **File format:** Word or PDF
- **References:** Suggest all references as in-text citations using AMA citation style, but other citation styles are accepted

The next page contains samples of funded AASM Foundation research projects that required a competitive LOI as part of the application process. The AASM Foundation thanks the Principal Investigators that generously provided their LOI for inclusion in this guideline.

**Principal Investigator:** Jennifer Albrecht, PhD

**Project Title:** *Impact of High PAP Adherence on Cardiovascular Outcomes Among Medicare Beneficiaries with Obstructive Sleep Apnea, 2006-2015*

**Funded AASM Foundation Grant:** 2018 Strategic Research Grant

## Introduction

Cardiovascular disease (CVD) is a leading cause of death and disability in the United States and worldwide. Importantly, between 40 to 60% of CVD patients suffer comorbid obstructive sleep apnea (OSA), which further impairs cardiac function and worsens patient-relevant CVD outcomes<sup>1-4</sup>. Although results have been mixed, evidence suggests that successful treatment of OSA can prevent future cardiovascular (CV) events, regardless of pre-existing CVD<sup>5,6</sup>. However, the beneficial effects of PAP are strongly related to PAP adherence, making interpretation of many studies difficult (e.g.,<sup>7,8</sup>). To advance understanding, there is dramatic need to evaluate the potential benefits of PAP therapy on patient-relevant CV outcomes among patients who have high PAP adherence. To this end the objectives of the proposed study are to evaluate the potential benefits of PAP on risk for CV events and increased healthcare utilization (HCU) among Medicare beneficiaries newly diagnosed with OSA. We will use the Medicare PAP adherence criteria to identify beneficiaries who demonstrate high PAP adherence and compare these individuals to beneficiaries who are non-adherent to PAP. To analyze risk for new CVD and CV events, we will create nested cohorts of beneficiaries with and without history of CVD. The Medicare population is particularly relevant because Medicare is the largest payer for medical care among the elderly in the United States and a leading developer of national health policy. Our team possesses expertise in CVD, OSA, PAP adherence, and the relevant Medicare dataset. We have over 100 publications related to CVD and OSA and are well-qualified and highly enthusiastic to complete the proposed study.

## Specific Aims and Hypotheses

The long-term goal of this research is to improve outcomes for patients with sleep disorders. The overall specific objective of the current application is to evaluate the impact of high adherence to positive airway pressure (PAP) on patient-relevant clinical outcomes in patients with newly diagnosed obstructive sleep apnea (OSA), with and without a history of cardiovascular disease (CVD). Our central hypothesis is that relative to low PAP adherence, high PAP adherence is associated with reduced risk of CV events and reduced health care utilization (HCU), regardless of CVD history. To achieve our objectives, we propose three specific aims:

Aim 1: To quantify the effect of high PAP adherence on risk of adverse cardiovascular (CV) events among Medicare beneficiaries with newly diagnosed OSA and without past CVD.

Hypothesis 1: Compared to non-adherence, high PAP adherence is associated with reduced risk of CV events.

Aim 2: To quantify the effect of high PAP adherence on risk of CV events among Medicare beneficiaries with newly diagnosed OSA and pre-existing CVD.

Hypothesis 2: Compared to non-adherence, high PAP adherence is associated with reduced risk of CV events.

Aim 3: To quantify the effect of high PAP adherence and HCU among Medicare beneficiaries with newly diagnosed OSA and pre-existing CVD.

Hypothesis 3: Compared to non-adherence, high PAP adherence is associated with reduced HCU.

## Methods

### *Data Source and Study Population*

The proposed study is a nested cohort study of a 5% sample of 2006-2013 Medicare administrative claims data obtained from the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Warehouse (CCW). First, we will create a cohort of beneficiaries newly diagnosed with OSA. OSA will be defined by applicable International Classification of Diseases - 9<sup>th</sup> Edition – Clinical Modification (ICD-9-CM) codes (327.23, 780.51, 780.53, 780.57). The date of first OSA diagnosis will be assigned as the index date. Second, we will identify beneficiaries with comorbid CVD. CVD will be defined by a standardized CCW algorithm for ischemic heart disease and/or a history of previous revascularization (i.e., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty). The CCW algorithm is based on ICD-9-CM diagnostic codes for acute myocardial infarction, old myocardial infarction, angina pectoris, and other forms of chronic ischemic heart disease. Third, we will create two nested cohorts, one with and one without pre-existing CVD. A beneficiary whose date of first diagnosis of CVD is prior to their index date for OSA will be placed in the nested CVD cohort. Beneficiaries whose date of first diagnosis of CVD is missing or occurs after the OSA index date will be assigned to the nested non-CVD cohort. To ensure sufficient follow-up to assess outcomes of interest and capture co-existing comorbidities, all beneficiaries will be required to possess continuous Medicare Parts A and B with no Part C coverage for 12 months pre-index date and 24 months post-index date.

### *Measures*

PAP Adherence.

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**CV Events.** CV events will be defined by ICD-9-CM codes representing myocardial infarction, stroke, heart failure, an acute ischemic event, and transient ischemic attack in any position on an inpatient or outpatient claim occurring after the OSA index date.

**Health Care Utilization.** HCU will be operationalized as rates (monthly, quarterly, and annual) of all-cause hospitalizations, emergency department (ED) visits, and outpatient visits occurring after OSA diagnosis. We will count events and person-time contributed to the exposed (i.e., high PAP adherence) group beginning with the OSA index date.

**Covariates.** The CCW contains dates of first diagnosis of 27 comorbid conditions and demographic characteristics in the beneficiary annual summary files. Comorbidities present at or prior to the OSA index date will be included in analyses.

### **Data Analysis Plan**

**Sample Size:** Based on preliminary analyses, there were 172,074 beneficiaries in the CCW diagnosed with OSA in 2011 with at least one year of continuous enrollment. Of these, we estimate that approximately 80% or 137,659 will initiate PAP therapy and 40-50% (55,064-68,680) of these will be high adherers. Even using very conservative estimates for the incidence of CV events, these large sample sizes will be sufficient to permit detection of even small effect sizes (Cohen's  $d = 0.2$ ) when assessing differences in CV events and healthcare utilization between high and low PAP adherers.

**Aim 1:** To quantify the effect of high PAP adherence on risk of CV events among Medicare beneficiaries with newly diagnosed OSA and without past CVD, we will assess risk of CV events occurring after the OSA index-date as a function of PAP adherence. Variables demonstrating significant association ( $p < .05$ ) with PAP adherence will be considered for inclusion in the final model. Cox proportional hazards models will be employed to test the adjusted association between high PAP adherence (compared to PAP non-adherence) and CV outcomes. First, we will model the unadjusted association between PAP adherence and risk of CV events. Next, we will add age, sex, and race into the model. The final model will be built by adding other covariates to the model and eliminating non-significant covariates. Hazard ratios and 95% confidence intervals will be reported.

**Aim 2:** To quantify the effect of high PAP adherence on risk of CV events among Medicare beneficiaries with newly diagnosed OSA and pre-existing CVD, we will perform similar analyses as in Aim 1, excepting that we will use the nested cohort of individuals with a history of CVD.

**Aim 3:** To quantify the effect of high PAP adherence and HCU among Medicare beneficiaries with newly diagnosed OSA and pre-existing CVD, we will compare high PAP adherers and non-adherers in rates of HCU during the year following OSA diagnosis. Counts of HCU events tend to be highly right skewed with many zero values. Thus, we will assess the fit of different distributions (e.g. negative binomial vs zero-inflated negative binomial) to model each HCU outcome prior to deciding on the appropriate regression approach. Next, we will fit separate models for each outcome, first by modeling the unadjusted outcome as a function of PAP adherence level and index year. The final model will be built by adding other covariates to the model and eliminating non-significant covariates. Effect estimates will be presented with their 95% confidence intervals.

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**I. Background:** Alzheimer's disease (AD) affects >5 million Americans, and without effective treatments or prevention strategies its prevalence will triple by 2050.<sup>12</sup> Identifying modifiable risk factors for AD is thus critically important.  $\beta$ -Amyloid ( $A\beta$ ) deposition and neurofibrillary tangles (NFTs) are the defining neuropathologic features of AD, but the factors facilitating the accumulation of these pathologies and the related cognitive decline remain largely unknown. Obstructive sleep apnea (OSA) is particularly prominent in AD, being more than five times more likely to be present in those with AD than age-matched healthy controls.<sup>13</sup> Moreover, presence of OSA has been shown to increase AD risk,  $\beta$ -amyloid and tau burden, and facilitate cognitive decline.<sup>1-8,14</sup> The precise mechanisms by which OSA increases AD risk, AD biomarker burden, and cognitive impairment remain unclear, however. Our group has identified reduced electroencephalographic (EEG) power during sleep in posterior brain regions in healthy, asymptomatic, treatment-naïve subjects with OSA compared to healthy controls.<sup>10</sup> This deficit was observed even during stable and deep NREM sleep with no respiratory events, hypoxia, or other signs of arousal. High density EEG (hdEEG) provides sufficient data to accurately model cortical sources of scalp EEG activity. Estimation of the sleep deficit in OSA showed remarkable overlap with default mode network (DMN) brain regions where our group and others have found peak amyloid deposition in preclinical AD.<sup>15-17</sup> Moreover, recent data show that deposition of amyloid in the DMN predicts reduced SWA in normal elderly without OSA,<sup>18</sup> suggesting an abnormality due to local sleep deficits. In OSA, it is unclear whether this deficit is related to hypoxia, given that these same areas show high aerobic glycolysis,<sup>19</sup> to repeated arousals from sleep due to OSA, or to AD pathology. Even more unclear is whether longitudinal OSA treatment in those at risk for AD with positive airway pressure (PAP) would ultimately mitigate local sleep deficits and the increase in AD risk associated with OSA, impact AD biomarker burden, and slow cognitive decline. Some findings support the notion that PAP treatment can delay the age of AD onset.<sup>6</sup> Preliminary proof of concept studies also showed that those using PAP for two years had lower AD biomarker burden than those who did not,<sup>5</sup> and a case report showed that PAP use for two years altered cerebrospinal fluid AD biomarkers, returning them to normal, non-AD levels.<sup>4</sup> Regardless, no longitudinal studies have examined the mechanisms linking OSA to AD, the efficacy of PAP treatment to slow AD biomarker progression, and the influence of PAP adherence on its efficacy to mitigate increased AD risk associated with OSA. **The overarching goal of this proposal is to determine the mechanisms linking OSA to AD biomarker burden and cognitive decline, and to characterize the efficacy of high PAP treatment adherence on longitudinal AD biomarker accumulation and cognitive decline over a two year period.**

## II. Specific Aims:

**AIM 1: Characterize the impact of baseline OSA severity on AD biomarkers, local sleep physiology, and memory in  $A\beta$ + cognitively asymptomatic older adults.** *Hypothesis 1:* Baseline OSA severity will predict magnitude of local sleep deficits, and these deficits will be due to either the severity of sleep fragmentation or hypoxia. *Hypothesis 2:* Baseline OSA severity will also predict DMN  $A\beta$  and medial temporal lobe (MTL) tau burden, as well as memory impairment, and this will be mediated by the extent of local sleep deficits.

**AIM 2: Determine the benefit of high PAP adherence for two years on local sleep physiology, AD biomarker burden, and memory in  $A\beta$ + cognitively asymptomatic older adults.** *Hypothesis 1:* PAP adherence (defined as mean hours of PAP use per night) over two years will predict the magnitude of longitudinal change in DMN  $A\beta$  and MTL tau burden, MRI-measured MTL atrophy, and memory decline. *Hypothesis 2:* The impact of PAP adherence on local sleep physiology will mediate the impact of PAP treatment on AD biomarker accumulation and memory decline.

## III. Approach:

Protocol and Participant Cohort: This proposal leverages existing resources at UCI, including a funded (P50 AG016573) Alzheimer's Disease Research Center (ADRC), and a funded R01 focused on PET and high resolution MR imaging of AD biomarkers (Co-I, Dr. Yassa: R01 AG053555). These resources include an existing cohort of 150 cognitively normal older adults (60-85yrs) not currently being treated for OSA and

enriched for A $\beta$  positivity (~50%) undergoing longitudinal neuroimaging of A $\beta$  and tau burden, as well as comprehensive assessment of AD-related MTL degeneration and memory decline. All cohort participants will be recruited and screened for OSA through at home sleep apnea testing devices. Those with at least mild OSA will undergo in lab polysomnography (PSG) with hdEEG. Based on population prevalence rates in this age group, we expect ~40-50% will meet the clinical criteria for OSA (AHI>5).<sup>20</sup> Those with OSA will be recommended the appropriate PAP treatment and will be followed over two years. PAP adherence data will be downloaded in 3 month intervals. All participants followed over two years will undergo a second in lab PSG with hdEEG within six months of their follow-up MRI and PET scans. A high rate of retention is expected, since subjects will be recruited from a cohort with highly motivated subjects that have been participating in ADRC sponsored neuroimaging studies of preclinical AD for years. An advantage of targeting this cohort is that subjects will have undergone collection of extensive longitudinal data, including baseline and follow up A $\beta$  and tau PET scans, high resolution MRI scans of MTL structure and function, APOE  $\epsilon$ 4 genotype, and a suite of sensitive pattern separation memory tests known to be sensitive to AD-related memory decline across the AD spectrum.<sup>21-23</sup> Integration with ongoing ADRC studies provides infrastructure, reduces the cost of the project and enables us to study the relationship between sleep and other markers of AD derived from comprehensive clinical evaluations, brain imaging (MRI and amyloid and tau PET), and neurocognitive tests, including longitudinal changes.

Polysomnography and high density EEG: hdEEG (256 channels) and standard PSG will be recorded simultaneously via an integrated system (Compumedics), following our standard procedures.<sup>10</sup> Subjects will be allowed to sleep for 8 hours during their usual sleep period. EEG, electromyogram and electrooculogram signals will be digitized at 500 Hz. Sleep stages will be visually scored in 30-s epochs according to standard criteria by a trained scorer, and studies will be reviewed for clinical sleep disorders by board certified sleep physicians.<sup>24,25</sup> Artifact-free epochs will be used for spectral analysis, quantified across the hdEEG array, with an *a priori* focus on SWA (1-4Hz) and sigma power (12-16Hz) due to their relevance for slow waves and sleep spindles.

#### IV. Data Analysis Plan:

Analysis of Aim 1: Hypothesis 1: Multiple regression analysis incorporating apnea/hypopnea index (AHI), sex, APOE genotype, age, number of arousals, and mean percent oxygen desaturation to predict local sleep deficits in SWA and spindle activity across the hdEEG array. Hypothesis 2: A similar model as in Hypothesis 1 will be used to predict DMN A $\beta$  and MTL tau burden, MTL volume and dysfunction, as well as memory impairment. Mediation analyses will be performed to determine whether local SWA and spindle activity deficits mediate the influence of OSA severity on AD pathology.<sup>26-28</sup>

Analysis of Aim 2: Hypothesis 1: This analysis will only be conducted in those that with AHI>5 detected at baseline. Multiple regression analysis incorporating baseline AHI, mean nightly PAP adherence over two years, sex, APOE genotype, age, number of arousals, and mean percent oxygen desaturation to predict longitudinal changes in local sleep deficits in SWA and spindle activity across the hdEEG array, DMN A $\beta$  and MTL tau burden, MTL volume and dysfunction, and memory. Hypothesis 2: Mediation analyses will be performed to determine whether longitudinal changes in local SWA and spindle activity mediate the influence of PAP adherence on AD pathology, MTL structure and function, and memory.<sup>26-28</sup>

**V. Cited literature:**

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GOSSELIN, Nadia

## **Title: Investigating sleep microarchitecture to better understand idiopathic hypersomnia pathophysiology mechanisms and phenotype heterogeneity**

### **Background**

Current gap: IH has poorly defined nosological entities and its pathophysiology is not well understood. This gap in knowledge has major consequences: it reduces our diagnostic abilities, prevent targeted therapy and impedes improvement in the patient's quality of life. One barrier to better understand its pathophysiology resides in the phenotypic heterogeneity and possible subtypes. These subtypes are poorly investigated and remain misunderstood. They include, among others, IH patients with or without comorbid depression/dysthymic symptoms and those with versus without objective markers of hypersomnia. We need to characterize these subtypes based on objective markers to improve diagnosis accuracy and develop individualized therapy.

Pathophysiological mechanisms: In the search for a better understanding of IH, sleep mechanistic is the most obvious candidate. The sleep microarchitecture elements are derived through advanced electroencephalographic (EEG) signal analysis. They have the potential to bring new information about the non-restorative aspect of sleep that is not available with EEG visual inspection. Frequently investigated microarchitecture elements are slow waves, sleep spindles, EEG spectral power in non-rapid (NREM) and rapid eye movement (REM) sleep, brain connectivity, and slow-wave activity dissipation. For example, brain connectivity metrics represent the brain's ability to disconnect and have a more restorative sleep [1]. Another example is the dissipation of the EEG slow wave activity that represents the sleep homeostatic process and how a patient can reduce its sleep pressure throughout the night [2]. These microarchitecture elements have been successfully used by our group and others in somnambulism [3], insomnia [4], REM sleep behaviour disorders [5], sleepiness associated with traumatic brain injury [6] and aging [7].

Limits of the literature: IH is not well characterized in terms of sleep architecture. According to a recent meta-analysis that included 10 studies, patients with IH have increased total sleep time and amount of REM sleep, but decreased sleep onset latency and amount of slow-wave sleep [8]. However, all studies except two included fewer than 20 IH patients. Regarding sleep microarchitecture, one study found increased sleep spindle density in IH compared to controls [9]. Given the role of sleep spindles in protection of sleep from arousal, authors hypothesized that the increased spindle activity across the night could explain sleep drunkenness in IH. Another preliminary study by our group showed that IH patients have lower NREM slow wave activity compared with controls [10]. Changes in slow-wave activity could be partly responsible for the increased sleep need and daytime sleepiness observed in these patients. Given the preliminary nature of these results, we need new studies with larger cohorts.

Opportunities/feasibility: Since 2000, our team has built a large clinical cohort of patients with IH. They all have two-week sleep diaries, one night of PSG, MSLT, questionnaires, body mass index, and medical history. 150 patients meet the diagnostic criteria for IH and 150 present hypersomnolence without objective markers. This cohort, combined with our expertise in advanced EEG signal analysis, offers a unique opportunity to characterize the microarchitecture signature of IH subtypes.

### **Specific aims**

We aim to characterize IH subtypes in order to better define their underlying pathophysiological mechanisms. To achieve this goal, we will characterize the sleep microarchitecture signature and sleep homeostatic pressure dissipation in different subpopulations of patients with a focus on 1) patients with versus without depressive/dysthymic symptoms and 2) with and without abnormal MSLT despite complaints of hypersomnolence. We will also assess how age, sex and body mass index impact their associated sleep microarchitecture and symptom presentation.

GOSSELIN, Nadia

## Methodological approach

**Participants:** We will include 300 patients (age > 16 years old) who are part of the Center for Advanced Research in Sleep Medicine database. For each patient, we have their age, sex, body mass index, the Epworth Sleepiness Scale, the Pittsburgh Sleep Quality Index, the Beck Depression Inventory, the medical history (including history of mood disorders), and medication. We will compare them to a group of 100 controls from our Montreal Archive of Sleep Studies databank, matched for age and sex.

**Criteria for IH:** 1) daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months, 2) cataplexy is absent, 3) fewer than 2 sleep onset in REM period (SOREMP) on MSLT or no SOREMP if the REM latency on the preceding PSG was  $\leq 15$  min, 4) mean sleep onset latency  $\leq 8$  min on MSLT or total 24 h sleep time is  $\geq 660$  min on wrist actigraphy or sleep log (averaged over at least seven days with unrestricted sleep).

**Criteria for hypersomnolence or subjective IH:** same criteria as IH, except mean sleep onset latency  $\geq 8$  min on MSLT and total 24 h sleep time is  $\leq 660$  min on wrist actigraphy or sleep log.

**Exclusion criteria:** apnea-hypopnea index > 10, neurologic disorder (e.g. Parkinson's disease, epilepsy, multiple sclerosis, moderate to severe traumatic brain injury, dementia, stroke), shift work, circadian rhythm disorders, sleep deprivation, other sleep disorders (e.g. somnambulism, restless leg syndrome, REM behaviour disorder, insomnia), medical conditions or medications that could explain hypersomnolence, and psychiatric disorder (e.g. schizophrenia, bipolar disorder) - those with anxiety or depression will have their symptom severity considered in the statistical analyses.

**Protocol:** Patients were asked to fill a sleep diary for two weeks before the PSG. PSG includes EEG (at least 4 electrodes), electrooculogram, submental electromyogram, electrocardiogram, bilateral anterior tibialis electromyogram, abdominal strain gauge, oronasal canula, video and audio recording, and transcutaneous finger pulse oximeter. MSLT is performed the day after and consists of 4 naps (10:00, 12:00, 14:00 and 16:00). This protocol was already approved by our ethic committee.

**Data analysis:** In addition to standard architecture variables, we will calculate EEG spectral power for N2, N3 and REM sleep for all frequency bands with a homemade software package [2]. Detection and morphological characteristics of spindles and slow waves will be automatically performed for N2 and N3 [6, 11]. Brain connectivity analyses using imaginary coherence between EEG electrodes will be performed in REM and NREM sleep [1, 3]. Slow wave activity dissipation will be performed by quantifying slow wave activity power for each NREM period [2]. All these analyses were previously used and described by our group.

**Statistical analyses:** We will use multiple linear regression analyses, with groups (objective IH, subjective IH, controls) and Beck Depression Inventory score as independent variables. Sleep macro and microarchitecture variables will be dependent variables. We will use age, sex and body mass index as interaction terms (moderators) in our statistical models. Anxiety symptoms will be a control variable.

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## **Background**

Narcolepsy is a rare, chronic neurological disorder with typical onset between ages 10-20 years<sup>1</sup>. Without well-controlled symptoms, pediatric narcolepsy patients may experience learning problems and academic failure<sup>2,3</sup>, increased risk of accidents<sup>4</sup>, depression<sup>5</sup> and challenges with relationships and self-identity<sup>6</sup>. However, validated outcome measures for children with narcolepsy to effectively assess disease management are scant.<sup>7</sup> Importantly, pediatric narcolepsy has distinct symptoms from adult-onset narcolepsy, limiting the utility of extending measures validated in adult patient population. Children with narcolepsy can have static cataplexy, unique manifestations of daytime sleepiness including hyperactivity and emotional lability, precocious puberty, and rapid onset obesity. Furthermore, emotionally triggered cataplexy may be treated differently in children/adolescents based on its functional impact. For instance, daily cataplexy may not be bothersome to a pediatric narcolepsy patient who is well adapted to symptoms vs. one who is bullied/avoids emotional triggers due to infrequent cataplexy. To ensure optimal clinical management of pediatric narcolepsy, new outcome measures are needed that capture both the frequency and functional impact of a broader range of symptoms. Thus the purpose of this study is to develop and validate a pediatric narcolepsy patient reported outcome scale (PN-PROS) for patients 8-17 years of age.

## **Specific Aims**

1. To develop pediatric narcolepsy item banks through expert interviews, review of existing literature and focus groups of pediatric narcolepsy patients (8-17 years).
2. To evaluate the content validity of the PN-PROS item pools.
3. To detect the treatment responsiveness of the item banks through a field test of the item pools in a diverse, national sample of pediatric narcolepsy patients (8-17 years).

## **Innovation:**

The proposed project will develop the first disease patient reported outcome measures for children and adolescents with narcolepsy, a rare disease that has significant functional impacts on patients. Additional innovations include: (1) the use of a novel, HIPAA compliant telehealth platform at Boston Children's Hospital to access pediatric narcolepsy patients across the United States for focus groups to generate items; (2) a partnership with patient advocacy groups including Wake Up Narcolepsy (WUN) and Project Sleep for more targeted patient recruitment ensuring a sufficient sample size; and (3) a unique collaboration between a pediatric narcolepsy expert with a patient population of 100 pediatric narcolepsy patients (KM), a mother of a child with narcolepsy and acting president of WUN (CC), a pediatric sleep psychologist with extensive experience in assessing neurobehavioral outcomes in children with a broad range of sleep disorders (LM), and leading authorities on the development and validation of patient reported outcome measures (DB and KB).

## **Methods/Analysis**

### **1. To develop pediatric narcolepsy patient reported outcomes item banks for children and adolescents (8-17 years).**

- PN-PRO item bank domains will be developed through 1) interviews with pediatric narcolepsy experts identified through the Sleep Research Network, 2) a comprehensive review of existing instruments, and 3) qualitative interviews with pediatric patients with narcolepsy and their parents/caregivers.

- Semi-structure interviews will be conducted in-person at Boston Children's Hospital (BCH, Boston, MA) and by telehealth with patients from Colorado Children's Hospital (CHCO, Denver, CO). We will conduct separate focus groups with pediatric narcolepsy patients ages 8-12 years (n=20) and patients 13-18 years (n=20). Interviews will be conducted separately with participants' primary caretakers. Patient diagnoses for narcolepsy type 1 and narcolepsy type 2 will be confirmed<sup>8</sup> prior to interviews through medical chart review.
- Interviews will be recorded and common themes extracted from developed transcripts using OpenCode online software. Domains may be further amended based on these interviews.
- Questions will be formulated based on identified domains, interviews, and literature review, and cognitive interviews will be utilized with n=25 pediatric narcolepsy patients for readability and comprehension. Items that are poorly understood will be removed or rewritten. We anticipate that questions will include Likert responses for both frequency of symptoms and functional effect of symptoms.

## **2. To evaluate the content validity of the PN-PRO item pools.**

- We will assess psychometric properties of the PN-PROS with item-total score correlations (item convergent validity). We will use factor analysis to assess the content structure of the survey.
- We will assess content validity by assessing associations with the Children and Adolescent Epworth Sleepiness Scores, Peds\_QL, and multiple sleep latency testing values (mean sleep latency and number of sleep onset REM periods) obtained from previously conducted diagnostic testing.
- We will further assess known-group validity by comparing PN-PROS scores between n=100 pediatric narcolepsy patients and n=100 pediatric patients with other sleep disorders. Participants will be recruited from BCH and CHCO, and ROC analyses will be used to examine sensitivity, specificity, and positive and negative predictive values.

## **3. To detect the treatment responsiveness of the item banks through a field test of the item pools in a diverse, national sample of pediatric narcolepsy patients (8-17 years) and their parents/guardian.**

- We will recruit 300 pediatric narcolepsy patients through Wake Up Narcolepsy website (estimated 1000 members are parents of pediatric narcolepsy patients), Project Sleep, and specified pediatric sleep clinics (BCH, CHCO). Diagnoses<sup>8</sup> will be confirmed through medical chart review. To determine treatment sensitivity of the PN-PROS, we will compare responses of participants 1) who are on pharmacologic treatments vs. those who are not, 2) who have medical records indicating a  $\geq 3$  point change in Epworth Sleepiness Score from time of diagnosis to present time vs. those  $< 3$  point change.
- We will reassess these patients with the PN-PROS 1 month later to determine reliability of the instrument.

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**Summary of Relevant Literature.** Obstructive sleep apnea (OSA) is a common and heterogeneous sleep disorder<sup>1</sup> with significant public health consequences. There is a well-established but complex relationship between OSA and cardiovascular (CV) disease,<sup>2</sup> the leading cause of death in the United States. Epidemiological evidence supports moderate to severe OSA as a cause of systemic hypertension and a risk factor for incidence and progression of stroke, coronary heart disease, heart failure and atrial fibrillation, and coronary and cerebrovascular mortality.<sup>3</sup> The physiological mechanisms explaining these associations are not completely understood.<sup>4</sup> Thus, there is limited accuracy in stratifying OSA patients according to their CV risk, which may explain the observed heterogeneity in the development of outcomes and treatment responses in clinical trials involving the use of continuous positive airway pressure (CPAP).<sup>5</sup> This is further complicated by the current characterization of OSA severity, which is generally limited to the apnea-hypopnea index (AHI), a single summary measure derived from diagnostic polysomnography (PSG).

There is enough evidence indicating the benefits of exploring other physiological characteristics derived from the PSG as a tool to phenotype individuals with OSA.<sup>6</sup> Such strategies have the potential to improve CV risk stratification and prediction of treatment response, while taking advantage of already existing PSG data. For example, a recent study using unsupervised clustering of conventional PSG metrics found that specific phenotypes were associated with higher combined risk of incident CV disease, while OSA severity classification based on the AHI was not.<sup>7</sup> While this study gained unique insights based on conventional PSG data, current advances in domain knowledge approaches are generating highly informative metrics about sleep (e.g. odds-ratio product,<sup>8,9</sup> arousal intensity<sup>10</sup>), airflow (e.g. loop gain,<sup>11</sup> arousal threshold<sup>12</sup>), respiratory events (e.g. event duration<sup>13</sup> and desaturation severity<sup>14,15</sup>), and autonomic characteristics (e.g. heart-rate variability and response to arousal,<sup>16</sup> cardiopulmonary coupling<sup>17</sup>). The ability of these metrics to identify clinically-meaningful groups of OSA patients with different CV risk profiles is promising, but remains to be investigated.

In addition, several signal processing techniques have been developed from an interdisciplinary time-series literature<sup>18</sup> that could be directly applied to raw PSG data, with the potential to expand clinical knowledge. It is possible to generate a large number of descriptive features to time-series data related to the distribution of values, how values are correlated through time, how the properties of the signal change over time, predictability of future measures, and other linear and nonlinear properties. Due to its high dimensionality, specific methods that translate these data into scientifically meaningful informative summaries are required, and fortunately available.<sup>19</sup> These data-mining methods have been successfully applied in other biological time-series,<sup>19,20</sup> but have not been applied to PSG data. Ultimately, these novel PSG time-series features may improve our ability to predict whether an individual patient has increased CV risk.

All of these approaches are underexplored tools to improve CV risk stratification in patients with OSA. Moreover, this wealth of information is not leveraged in clinical practice, mainly because there are no methods that easily translate the physiological data into understandable and actionable information. Thus, this study will use existing signal processing techniques to expand the current knowledge of OSA cardiovascular pathophysiology and develop tools to bridge the gap between PSG characteristics and clinical care. To achieve this goal, we will use existing baseline and follow-up demographic, clinical and PSG data from the Sleep Heart Health Study<sup>21,22</sup> and propose the following **Specific Aims**:

**Aim 1: Identify the best predictors of adverse CV events in OSA using conventional and novel PSG metrics.**

- 1A)** Validate the use of conventional PSG metrics to predict incidence of CV events using supervised machine learning.
- 1B)** Determine if novel domain knowledge PSG metrics improve prediction of the incidence of CV events.
- 1C)** Determine if a comprehensive set of time-series features, derived from each PSG signal, improves prediction of CV events using an automated feature extraction and selection platform.

**Aim 2: Translate the established high-dimensional PSG predictors of CV outcomes into clinical knowledge.**

- 2A)** Combine the PSG-derived predictors of incident CV events with known CV risk factors in OSA and perform an unsupervised cluster analysis to identify PSG physiological subtypes with differences in CV pathophysiology.
- 2B)** Characterize the demographic, physiological, and clinical aspects of the identified subtypes.
- 2C)** Validate the ability of the PSG physiological subtypes to accurately predict CV outcomes and risk.

**Aim 3: Develop an automated computational framework that offers a user-friendly “PSG-to-CV-risk” solution to assist clinicians in interpreting PSG physiological information related to the CV risk of an individual OSA patient.**

This project has the potential for **high-impact on patients and clinicians**, as it represents a crucial and innovative step towards utilizing the immense amount of data available in the PSG for a clinically applicable precision medicine approach to cardiovascular risk assessment in OSA.

**Summary of Study Methods.** To achieve the proposed Specific Aims, we will use data from the Sleep Heart Health Study (SHHS), a multi-centric prospective community-based cohort study of adults aged  $\geq 40$  years, originally designed to assess the cardiovascular consequences of sleep disordered breathing, as described extensively elsewhere.<sup>21</sup> The study consisted of two visits approximately 4-5 years apart that included in-home PSG using the Compumedics P-series portable monitor (Abbottsford, Australia). The following signals were recorded: electroencephalogram (EEG), electrooculogram, submental

electromyogram, thoracic and abdominal excursions, nasal-oral thermocouple, pulse oximetry, electrocardiogram, heart rate, and body position.<sup>22</sup> We will use PSG, clinical and demographic information on 5,802 men and women, with available data from visit 1 and cardiovascular outcome records up to 13 years. Data access was granted through the National Sleep Research Resource.<sup>23</sup> We will initially extract the conventional PSG measures, including various event frequency indices, oxygen saturation measures, sleep latency and efficiency, and percentages of time spent in different sleep stages (**Aim 1A**). We will then derive a list of novel metrics based on physiological studies about sleep and airflow dynamics, respiratory event characteristics and autonomic responses for each individual with valid, high quality PSG signal data. These expanded metrics include variables related to EEG spectral power characteristics, odds-ratio product, arousal and respiratory arousal characteristics, average duty cycle, flow limitation, loop gain, severity and duration of respiratory events, heart-rate variability and response to arousal, and cardiopulmonary coupling (**Aim 1B**). Finally, we will use a well-established computational framework for automated time-series feature extraction, implemented in the software *hctsa*,<sup>19</sup> to compute over 7,700 time-series features for each signal (e.g. EEG, airflow). The extracted features include summaries of the distribution of values in the data, autocorrelation structure, stationarity, information theory measures, linear and nonlinear model fits to the data<sup>18</sup> (**Aim 1C**). This comprehensive list of PSG-derived parameters will be evaluated as potential predictors of incidence of the following CV events and outcomes: any cardiovascular disease (n=1,196), fatal cardiovascular disease (n=359), coronary heart disease (n=793), fatal coronary heart disease (n=235), stroke (n=287), myocardial infarctions (n=360), atrial fibrillation (n=332), and all-cause mortality (n=1,305), where n represents the number of individuals with events. Other relevant demographic and clinical data include age, sex, race and ethnicity, body mass index, anthropometric measurements, blood pressure, smoking and alcohol use, diabetes mellitus and Epworth Sleepiness Scale.

**Summary of Data Analysis Plan.** **Supervised Machine Learning:** This proposal will explore different supervised classification algorithms to identify the best prediction models of incident CV events using conventional (**Aim 1A**) and novel (**Aim 1B**) PSG metrics, and an extended set of time-series features from raw PSG signals (**Aim 1C**). Since the input PSG metrics for Aim 1A-B are derived from domain knowledge (i.e. physiological studies support their role in OSA and CV pathophysiology), no *a priori* feature selection will be performed and a more flexible set of classification algorithms can be investigated (Naïve Bayes, Support Vector Machine, Linear Discriminant Analysis, Decision Trees, Random Forests, Neural Networks, Logistic Regression and Rule-based Learning Classifier Systems), as implemented in the R package *mlr*<sup>24</sup> and software *ExSTraCS*.<sup>25</sup> For Aim 1C, given the large number of features, we will use the framework provided in the software *hctsa*,<sup>19</sup> which includes filtering and normalization of the resulting time-series feature vector (i.e. the calculated parameters from the raw PSG signal), followed by a time-series classification task using Support Vector Machine. After establishing the model, the linear classification accuracy of each feature will be compared to the mean linear classification accuracy using all features, and to a set of permuted class labels, and finally ranked to establish the top contributors to the prediction of CV events. The top features will be further investigated according to their time-series domain and relevance to the underlying physiology. All classification tasks will be evaluated using 5 to 10-fold cross-validation, according to sample size. The model predictive performance will be evaluated by the prediction accuracy, sensitivity, specificity, negative predictive value and positive predictive value. **Unsupervised Clustering:** Once the best prediction models and most discriminative PSG metrics are established, we will use unsupervised clustering to define subgroups of individuals with differential CV risk profiles according to their PSG characteristics, and other relevant clinical information (**Aim 2A**). We will perform a variable clustering and selection step to identify features with minimal correlation, while maintaining most of the variance in the dataset and the interpretability of the results.<sup>7</sup> The correlation structure of the remaining variables will be investigated and weights will be applied for highly correlated variables. A systematic approach to identify the optimal clustering method and the most robust underlying classes will be used,<sup>26</sup> in addition to clinical interpretation and significance. **Characterization of identified clusters:** To describe the clinical relevance and interpretability of the resulting clusters (i.e. PSG physiological subtypes), we will verify their associations with clinical and demographic factors using analysis of variance (ANOVA) or Kruskal-Wallis tests. Categorical variables will be compared using Chi-squared or Fisher's exact tests (**Aim 2B**). To provide a clinically interpretable prediction model of CV risk, we will use cluster membership as a predictor of CV event incidence using logistic models, and time to CV event will be analyzed using Cox Proportional Hazards survival analysis (**Aim 2C**), adjusted for appropriate covariates. **Development of computational framework:** As a consequence of the application of the above methods, and given the critical need for an automated solution that translates raw PSG signal data into accurate clinically actionable CV risk predictions, we will develop a user-friendly "PSG-to-CV-risk" platform that automates the several signal processing steps used to extract relevant information from the PSG (**Aim 3**). Additionally, the platform will aid the interpretation of the complex source of data into a comprehensible and clinically relevant CV risk category, according to the results of the present proposal. We plan to combine different computational frameworks to connect the stages of data processing and result reporting: PSG recording signal extraction (MATLAB®), conventional and novel domain knowledge metrics (C#), comprehensive time-series features (MATLAB®), machine learning prediction models (MATLAB® and R), subtype membership (R) and clinically interpretable CV risk



**Principal Investigator:** Diego Mazzotti, PhD

**Project Title:** *Leveraging Polysomnographic Physiological Signals for Improved Cardiovascular Risk Stratification in Obstructive Sleep Apnea*

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prediction (R). Finally, using R Shiny, we will develop a single interface readily accessible for clinicians, allowing the efficient and comprehensive analysis of PSG with potential extension for the prediction of CV risk.

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Current evidence-based treatment guidelines for narcolepsy from the American Academy of Sleep Medicine (AASM) give the highest level of recommendation to modafinil and sodium oxybate, with a lower level of evidence supporting use of methylphenidate and amphetamine-based stimulants [1]. However, clinical use of central nervous stimulants is widespread, and very few data are available to guide clinical decision-making regarding the decision of which medication should be prescribed for which patient. Considering idiopathic hypersomnia, only three randomized controlled trials of any medication have been published [2-4], none using methylphenidate or amphetamine-based stimulants, and no FDA-approved therapies exist. This lack of data on central nervous system stimulants complicates shared decision-making and frequently results in the denial of medication coverage, severely limiting treatment options.

Although explanatory, randomized, controlled trials (RCTs) are the gold-standard for assessing efficacy, they are frequently insufficient to guide clinical practice because of narrow inclusion/exclusion criteria and comparison to a placebo rather than to a real-world clinical alternative. Enrollment is limited to those patients whose symptom severity is such that they can commit to a placebo treatment for the study, which excludes many patients seen in clinical practice. In contrast, trials that incorporate degrees of pragmatism [5] can help overcome some of these obstacles to increase generalizability and more clearly guide clinical practice.

In addition to a focus on trial design that supports key clinical decisions, pragmatic studies emphasize the use of outcomes that are important to patients and other stakeholders. To date, RCTs for central disorders of hypersomnolence have predominantly focused on excessive daytime sleepiness. While this is undeniably the core symptom of these disorders, other symptoms may be equally or more problematic for patients. Among people with narcolepsy in the Nexus Narcolepsy Registry, 57.1% cited difficulty concentrating, focusing, or thinking as a reason they initially sought medical evaluation for narcolepsy [6]. Ancillary symptoms may not be well managed by current treatments. Among 249 patients with idiopathic hypersomnia in the Hypersomnia Foundation Registry, patients receiving treatment were only modestly less likely to experience daily difficulty with sleep inertia than were untreated patients (61.1% vs 74.4%). Treated and untreated patients had similar rates of subjective cognitive brain function (“brain fog”, 58.8% vs 58.1%) (Trotti LM, unpublished data).

To address the limitations in current evidence for the treatment of central disorders of hypersomnolence and better guide shared clinical decision-making, we propose a pragmatic clinical trial comparing modafinil and amphetamine salts in patients with narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia.

**Aim 1:** To compare the effectiveness of modafinil and amphetamine salts in patients with central disorders of hypersomnolence. Primary outcome will be Epworth Sleepiness Scale score, with a co-primary outcome to be determined in collaboration with patient stakeholders. Secondary outcomes will include subjective cognitive dysfunction, sleep duration, sleep inertia, and other outcomes identified by stakeholders.

**Aim 2:** To compare safety of modafinil and amphetamine salts in the treatment of central disorders of hypersomnolence.

**Aim 3:** To evaluate for clinical predictors of response to each medication.

**Methods:** Primary outcome for Aim 1 will be change in sleepiness as measured by the Epworth Sleepiness Scale. The co-primary outcome will be selected based on feedback from patient stakeholders to identify patient-oriented outcomes of most importance. Such stakeholder input will be sought from patient groups (Hypersomnia Foundation, Narcolepsy Network) prior to finalizing study protocol; Drs. Trotti and Rye have longstanding relationships with these organizations. This proposal was submitted for an ASMF 2017 strategic research award. If it is not funded but feedback from the reviewers is available, we will modify this 2018 proposal to address the concerns of the reviewers.

Treatment-naïve patients seeking evaluation for central disorders of hypersomnolence at our sleep disorders clinic, which sees over 900 patients for hypersomnolence disorders annually, will be invited to participate and randomized to one of the treatment arms upon consent. Although pragmatic trials often do not involve blinding to condition, those trials where outcomes of interest are primarily subjective often require blinding to minimize bias [7], which will be necessary in this case. Randomization, allocation concealment, blinding, and medication dispensing will be managed by Emory’s Investigational Drug Service.

**Principal Investigator:** Lynn Marie Trotti, MD, MSc

**Project Title:** *Informing Treatment Decisions in the Central Disorders of Hypersomnolence: A Pragmatic Clinical Trial of Modafinil Versus Amphetamine*

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Inclusion criteria will be a diagnosis of: narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, hypersomnia comorbid to psychiatric or medical disease [8], and unspecified hypersomnolence. The latter diagnosis will encompass patients who are clinically judged to have a central disorder of hypersomnolence but do not meet PSG/MSLT criteria, as this situation is commonly encountered in clinical patient series [9, 10]. Exclusion criteria will include an allergy or contraindication to the study drugs.

Outcome measures will include: Epworth Sleepiness Scale, sleep log for total sleep time, Sleep Inertia Questionnaire [11], a visual analog scale of difficulty awakening in the morning, a visual analog scale of cognitive dysfunction/"brain fog", adverse events, and other outcomes as identified as key by stakeholders. These measures are routinely incorporated into our clinical practice. Measures will be collected at baseline, week 4, week 8, and week 12. Week 4 and 8 measures will be collected remotely from patients using the electronic, HIPAA-compliant RedCAP data collection system. Baseline and week 12 measures will be collected in a face-to-face visit, mimicking the frequency of follow up in routine clinical practice.

Medications will be provided initially as: modafinil 100 mg qam and amphetamine salts 10 mg qam. For patients reporting difficulty awakening at baseline, the first dose will be taken 1 hour before planned awakening, whenever possible. For patients without difficulty awakening at baseline, first dose will be taken upon awakening. Patients will be advised to increase dosage once a week with the following schedule: week 2, 1 pill qam and 1 qnoon; week 3: 2 pills qam and 1 qnoon; week 4 and beyond: 2 pills qam and 2 pills qnoon. Patients will be instructed not to titrate further once they feel symptoms are well-controlled, and to reduce dosage one step in the case of side effects (other than severe).

Effectiveness of the interventions at week 12 compared to baseline will be determined separately for each outcome, initially via t-test of change from baseline scores in the two treatment groups, then via regression to allow for inclusion of relevant clinical features (diagnosis, MSLT results, sex/gender, etc). Secondary analyses will consider predictors of treatment response (decrease in ESS of  $\geq 4$  points, reduction in other scales by 50%) and response at different treatment intervals (i.e., weeks 4 and 8). Although the investigative team has extensive clinical trial and statistical experience, additional statistical consultation will be provided through Emory's CTSI consultation program.

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