Study Protocol: Sleep Disordered Breathing in Chronic SCI: A Randomized Controlled Trial of Treatment impact on Cognition, Quality of Life, and Cardiovascular Disease

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Background

Spinal cord injury (SCI) is universally recognized as a catastrophic disability impacting every aspect of life. The incidence of SCI within the US military is currently 429 per million person years,[1] significantly higher than the civilian population. Disability from SCI exerts significant emotional, personal, economic, and social burdens.[2,3] Most people with SCI sustain their injuries in their third or fourth decade of life, and lifespan after SCI remains significantly foreshortened. Medical co-morbidities including cardiovascular disease (CVD) have emerged as leading causes of mortality in chronic SCI with a prevalence exceeding non-disabled individuals, and an accelerated trajectory in early life. [4] Prevalence rates of asymptomatic and symptomatic CVD in SCI populations range from approximately 25% to more than 50%. In contrast, among age-matched non-disabled populations the prevalence of CVD is typically reported to be in the range of 5–10%.[5]

In addition to medical complications, 10 - 60% of individuals with SCI experience co-morbid cognitive impairments in the areas of processing speed, attention, memory, and cognitive flexibility.[6-9] Cognitive impairments prolong near-term and chronic adjustment to disability, and delay learning of new skills. An emerging clinical challenge is the management of these medical, psychological and cognitive long-term sequelae of SCI.

An area that has garnered little attention in the SCI arena is the role of sleep disorders on psychological, cognitive, and physical health. People with SCI report higher rates of subjective sleep disturbances than the general population, particularly restless sleep, early morning awakenings, muscle spasms, daytime sleepiness, and snoring.[10] In the general population, sleep disorders, and poor sleep quality adversely impact CV health, mood, emotional well-being, cognition, and health-related quality of life (HRQOL).[11-13] In particular, sleep disordered breathing (SDB), characterized by periods of complete cessation of breathing (apnea) or marked reductions in airflow (hypopnea), sleep fragmentation, and frequent oxygen desaturations, is associated with impaired cognition, depression, greater susceptibility to pain, increased risk of stroke, hypertension, atrial fibrillation, diabetes, and perhaps even mortality in the general population.[14-19]

A) Prevalence of Sleep Disordered Breathing in Persons with Spinal Cord Injury

Small cross-sectional studies in persons with SCI report SDB prevalence rates ranging from 27-62%, depending on the acuteness of, and level of injury; **these rates are 2-5 times higher than the general population.**[20-22] In a longitudinal study of patients with tetraplegia, sleep apnea was present in 60% of subjects within four weeks of injury, reaching a peak incidence of 83% three months after injury.[20] In cross sectional studies conducted by our team, the prevalence of obstructive sleep apnea (OSA-subset of SDB) ranged from 56% in those with incomplete tetraplegia to as high as 91% in those with complete lesions (cited reference and preliminary data).[23] **Given the many health and cognitive consequences related to SDB, it is imperative to determine the health impact of this disorder in the SCI population which is already at risk for many of the same secondary medical complications of SDB (e.g. diabetes, cardiovascular disease, poor memory and concentration).**

The prevalence of SDB in SCI is considerably higher than general population estimates of 2-4%.[24] Unfortunately, there is a paucity of information on the underlying reasons for this increased prevalence and more research is needed in this field. Obesity is an important risk factor for SDB. Among the 6 million users of Veteran Health services, an alarming 2/3 of women and 3/4 of men are overweight or obese. [25] A retrospective review of 7959 veterans with SCI reported that 37% were overweight and another 31% obese.[26] Additionally, people with tetraplegia have an increased neck circumference and spend more time sleeping supine, both known risk factors for SDB in the general population. However, these factors do not fully explain the increased prevalence of SDB in persons

with SCI.[27] In their 2001 retrospective, case–control study of 53 SCI individuals, Burns et al. demonstrated that obstructive sleep apnea in tetraplegia is associated with obesity and a higher cervical cord level but not with ASIA impairment.[21] In 2002, Stockhammer et al. demonstrated that SDB was significantly correlated with age, body mass index (BMI), neck circumference, and time after injury but not with lesion level or ASIA impairment.[28] Berlowitz, et al. have shown that in those with acute tetraplegia, SDB is present at a lower BMI than their non SCI counterparts.[29] This suggests the interplay of several mechanisms that increase the prevalence of SDB in SCI. Interestingly, SCI patients with SDB require significantly less positive airway pressure (PAP) therapy at any given SDB severity compared with able-bodied individuals with sleep apnea.[29]

Emerging data demonstrates that the prevalence of SDB in SCI is increased. Additionally, the characteristic risks for, and subsequent response to therapy likely differs from the general population and deserves dedicated research to determine the nature and significance of SDB and its treatment in SCI

B) Cognitive and Quality of Life Consequences of SDB

The cognitive functions most frequently and reliably reported as being affected by SDB in the general population, are vigilance, attention, memory, executive and motor functioning.[30,31] A meta-analytic review suggests that obstructive sleep apnea (OSA) has a moderate to severe impact on vigilance, motor coordination, and executive functions, while there is little effect on intelligence, verbal, and visual-perceptual abilities.[32] Many of the studies are limited by relatively small sample sizes, non-comprehensive cognitive test batteries, and inadequate control groups.

Cognitive deficits in information-processing, speed, attention, memory, and executive function are also commonly reported post SCI.[6-8,33] **The intermittent hypoxia and frequently disrupted sleep associated with untreated SDB may worsen already existing cognitive deficits in the subset of patients with both SCI and SDB, leading to sub-optimal cognitive outcomes in this unique patient population. Cardiovascular disease (seen commonly in chronic SCI and in SDB) likely also plays a role in this cognitive decline.[34]** Sajkov, et al,[35] studied the effect of SDB on neuropsychological functioning in 37 tetraplegic patients at least 6 months post injury. Thirty percent (11 of 37) had moderate to severe SDB. Neuropsychological measures of cognitive ability were significantly correlated with measures of sleep hypoxia, with deficits cited in attention, concentration, memory and learning. Further, cognitive impairments sustained by subjects with tetraplegia were both statistically and clinically significant when compared with non-disabled population values. **These deficits are likely to substantially prolong rehabilitation, reduce future independence, and limit vocational outcomes following injury; all of which are essential benchmarks for successful community re-entry after injury.**

Several studies have demonstrated that individuals with SDB in the general population have a lower quality of life, than age- and gender-matched controls. SDB effects many different aspects of a person's life, including physical, emotional, and social well-being.[36] In a community sample of SCI individuals, Berlowitz, et al determined that the self-reported quality of life and health utility scores in individuals with SCI and SDB were very low when compared with Australian population norms and correlated with severity of SDB. **The large reduction in health status attributable to SDB, especially in those with complete lesions, suggests that effective, well-tolerated treatments for SDB have substantial potential to improve quality of life in this population**.[23]

C) Cardiovascular Consequences of SDB

In the general population, considerable evidence points to the association between SDB and cardiovascular disease. This association is particularly strong for systemic hypertension, observed in

large population studies.[16,37] In the Sleep Heart Health Study cohort, sleep apnea was found to be an independent risk factor for coronary artery disease (CAD), congestive heart failure, cerebrovascular disease[38], and cardiac arrhythmias, including atrial fibrillation and complex ventricular arrhythmias.[39] Additionally, long-term outcome studies of patients with CAD have demonstrated higher cardiovascular mortality in patients with sleep apnea compared with those without, even after controlling for important risk factors such as age, weight, and smoking.[40]

The pathophysiological mechanisms of cardiovascular morbidity in SDB are complex and related to the repetitive episodes of intermittent hypoxia, sleep fragmentation and sympathetic surges observed in those with sleep apnea. Oxidative stress is a major component in the chain of events leading to atherogenesis and cardiovascular morbidity in SDB. [41] Oxidative stress alters signalling pathways and activates inflammatory and immune responses via increased interactions of blood cells with endothelial cells, facilitating endothelial cell injury and dysfunction. Such events can promote atherosclerosis and the development of cardiovascular morbidities in sleep apnea.[42] Figure 1 illustrates the proposed pathogenetic mechanisms leading to the CV consequences of SDB.

A number of biomarkers, linked with CVD, are also elevated in patients with SDB including an increased expression of pro-inflammatory cytokines such as TNF-α, IL-6, and hs-CRP.[41] Several measures of oxidative stress have been proposed in the study of molecular mechanisms of SDB causing CVD. From the many candidates available, the best currently available biomarker for oxidative stress, and the one most accepted in the field is 8-isoprostane (8-iso-PGF2α), a marker of lipid peroxidation.[43] Isoprostane metabolites in urine are stable and have been found to be an accurate way to measure oxidative stress in humans.[44]

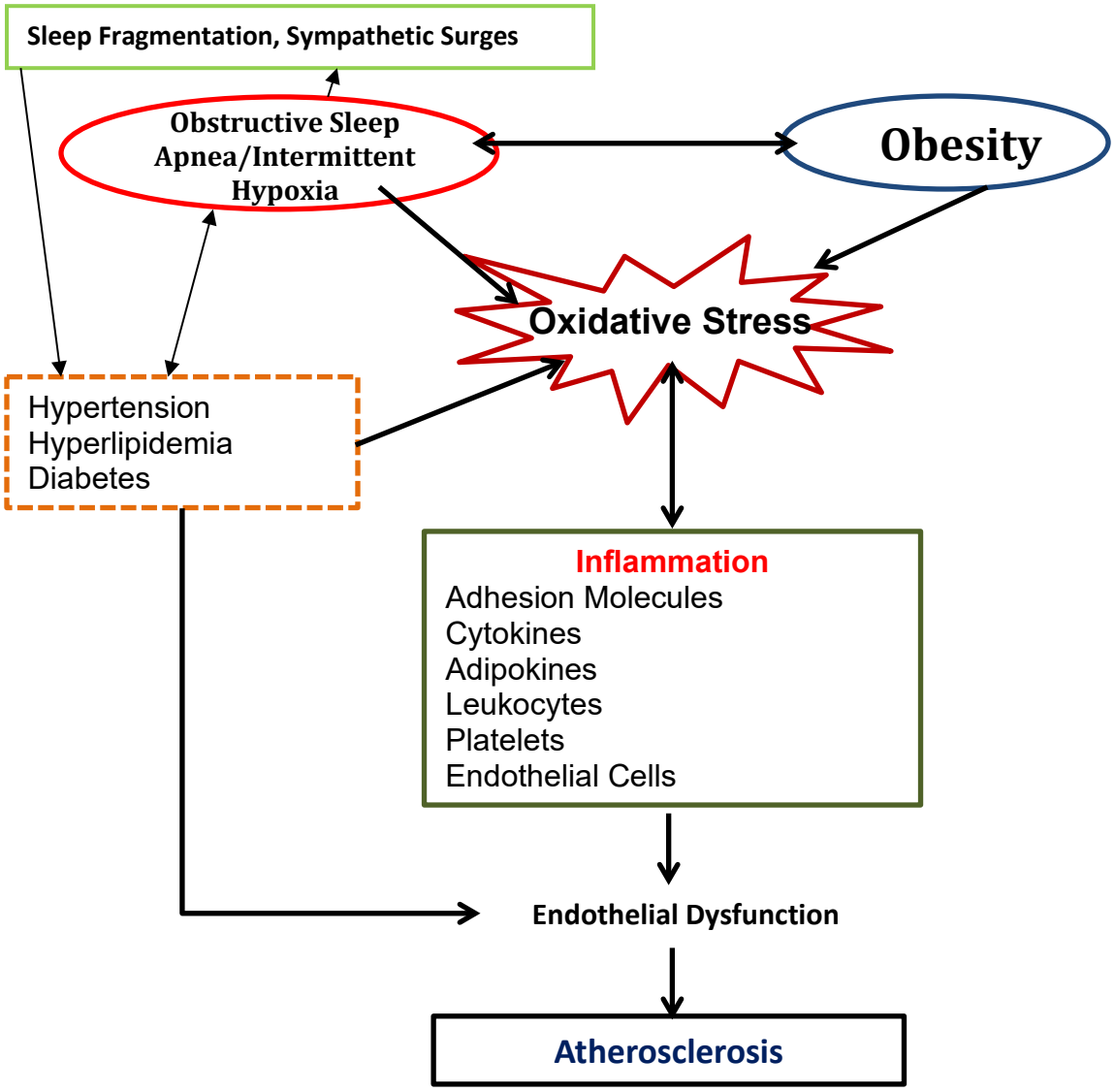
Cellular adhesion molecules, which promote adhesion of circulating leukocytes to endothelial cells and endothelial dysfunction, are potentially one of the first steps in the pathogenesis of atherosclerosis.[45] The release of cellular adhesion molecules can be stimulated by inflammatory cytokines, and oxidative stress, both increased in SDB. A variety of cellular adhesion markers, such as ICAM-1, vascular adhesion molecule-1 (VCAM-1), E-selectin, and L-selectin, have been shown to be elevated in sleep apnea compared to controls. [46,47]

Oxidative stress, inflammation, and sympathetic activation can all affect the expression of adipokines, molecules released by metabolically active white adipose tissue.[43] One such adipokine, adiponectin, has an anti-inflammatory function as it inhibits production of IL-6 and TNF-α.[48] Oxidative stress, TNF-α, and IL-6 all inhibit adiponectin production and thus potentiate their own pro-inflammatory effects. Adiponectin levels have been shown to be lower in sleep apnea patients compared to BMI-matched controls.[49,50] A decrease in adiponectin levels is associated with obesity, insulin resistance, type 2 diabetes, and CVD.[43,51] The biomarkers that are chosen in this study are thus representative of key pathways in the proposed model of atherogenesis and have been associated with CVD.

D) Treatment of Sleep Apnea and Its Impact on Cognitive Measures in the General Population

Positive airway pressure therapy (PAP) has emerged as the most effective therapy for SDB in the general population. PAP is administrated by a small motorized unit that pushes pressurized air through a hose attached to a mask strapped to the patient's face. PAP works as a "pneumatic splint" by delivering a positive intraluminal pressure, alleviating the episodes of upper airway collapse characteristic of sleep apnea. PAP is an effective means of normalizing breathing, and eliminating the repetitive deoxygenation-reoxygenation cycles thought to be responsible for the oxidative stress burden of SDB. [52-54]

Figure 1. Proposed Mechanisms for Cardiovascular Disease in Sleep Apnea[42]



PAP has been shown to improve some but not all cognitive deficits noted in persons with sleep apnea in the general population.[31] Several studies have shown that post PAP therapy, cognition has improved in the areas of memory[55], sustained attention [56], motor speed, and executive function [57,58]. However, other studies suggest no or minimal improvement in a battery of cognitive measures.[31,59,60] Studies in this area are heterogeneous and vary by population characteristics, methodology, design, severity of SDB, duration of PAP prescription, and compliance with therapy. One hypothesis that has emerged from these conflicting reports on PAP and cognition is that PAP only partially reverses measured cognitive deficits. The reasons for this partial reversibility is not entirely clear but may be due to the lack of sensitivity of existing cognitive measures and/or structural changes in the brain that are no longer reversible.[61] **Arguably individuals with chronic SCI differ from the general population in their medical co-morbidities contributing to cognitive decline as well as their baseline neuro-psychological vulnerabilities.** The treatment of SDB in this unique population may have a significant beneficial impact on cognitive function. Indeed there is limited evidence in the literature that suggests in other conditions with baseline cognitive deficits, treatment of SDB may lead to some improvement in cognitive performance.[31] In a randomized trial of PAP treatment in mild Alzheimer's disease, following 3 weeks of PAP treatment, general cognitive performance improved within a subset of patients with Alzheimer's and sleep apnea.[62] Subsequent analysis suggested those

with Alzheimer's and SDB who were adherent to PAP had a slower cognitive decline, especially in the domain of executive function and processing speed, exhibited stabilization of depressive symptoms and daytime somnolence, and showed significant improvement in subjective sleep quality.[63] **Our proposal is the first to evaluate the impact of PAP therapy on cognitive measures in chronic SCI.**

E) Impact of PAP on Cardiovascular Measures in the General Population
In the general population, there is a growing body of literature that demonstrates the effectiveness of PAP in improving systemic blood pressure [64] and several longitudinal observational studies showing that PAP therapy is associated with decreased fatal and non-fatal cardiovascular events.[15,65] Additionally, PAP has been shown to reduce biomarkers of oxidative stress and inflammation.[43] Most studies report a reduction in TNF-α, IL-6, and hs-CRP within 2-4 weeks of therapy; [66,67] a few show no effect. Obesity, cardiovascular disease, smoking status, asthma, and other inflammatory conditions confound the association between SDB and systemic inflammation; many of the studies that do not report any improvement in inflammatory biomarkers with PAP may not have adequately addressed these confounders. Two small studies have given conflicting results about effects of PAP on adiponectin levels. One found an increase in adiponectin levels after 14 days of PAP therapy [68] while another observed no change from baseline levels.[69] Adhesion molecules including VCAM-1 have been shown to decrease with PAP therapy.[70]

The SCI population is uniquely at risk for chronic inflammation. Studies in SCI have shown elevated hs-CRP levels in addition to increased VCAM-1, endothelin-1, and IL-6 levels.[71] The crossroads of SCI and SDB may well represent an elevated pro-inflammatory state that predisposes to CVD disease burden. Reducing systemic inflammation is likely to be beneficial. **There is no information on the impact of PAP therapy on these inflammatory markers in the SCI population with SDB. Our proposal is the first to evaluate this association and determine the therapeutic impact of PAP in this uniquely vulnerable population.**

F) Impact of PAP on Mood, Sleep Quality, and Quality of Life in the General Population
There is limited information on the effect of PAP on mood in patients with SDB and the results have been mixed, with some studies reporting improvement [72] and others showing no significant effects.[56] However, these studies were limited by small sample size, and use of differing indexes of mood, and heterogeneous controls. Several small studies have documented significant improvement in quality-of-life measures following PAP treatment in patients with sleep apnea.[56,73,74] The most recent Cochrane systemic review included 36 trials of PAP therapy and 1718 people. Study quality was mixed. Compared with control (sham or no therapy), PAP showed significant improvements in objective and subjective sleepiness and several quality of life, cognitive function, and depression measures.[75] **In a condition where functional recovery has remained elusive, interventions that improve quality of life, daytime functioning, and cognition will play an important role in overall well-being of individuals with SCI and improve social, vocational, and emotional interactions.**

Our cumulative pilot data indicate that sleep complaints and disorders are prevalent in individuals with SCI and likely play an important role in physical and psychological well-being. It further highlights the increased prevalence of SDB, and the need to systematically study the impact of SDB on cognitive and cardiovascular health in individuals with SCI, as proposed in this application. The ease of applying the technology with minimal technical difficulties, coupled with the strong expressed preference for at home studies, supports our decision to use portable PSGs in this proposal. **Our proposal builds upon our experience with acute SCI and extends it to study cognitive and cardiovascular variables in those with chronic SCI. This is the first proposed clinical trial that explores the impact of PAP therapy on cognitive and cardiovascular measures in participants with chronic SCI and SDB.** Our team has extensive clinical experience in the diagnosis and management of SDB in SCI. We have studied the prevalence of SDB in acute and chronic SCI and

have determined the feasibility, safety, and challenges of PAP use in this population. We have recently measured cardio-metabolic changes pre and post PAP in chronic SCI and cognitive changes with PAP in acute SCI. **These preliminary data form the basis for the much needed proposed study, a multi-center prospective, double-blinded randomized controlled trial (RCT) designed to determine the impact of four months of PAP therapy on cognitive and CV measures in persons with chronic SCI.**

G) Study Relevance and Applicability of Proposed Findings

There is a paucity of information on the impact of SDB and its treatment in chronic SCI. Despite the increased prevalence of SDB in SCI, screening for SDB and its treatment are not yet standard of care. To enable change in practice, well-designed RCTs are needed to demonstrate the importance of SDB and its treatment in the health of this population. The following is a summary of perceived knowledge gaps and the beneficial impact of our proposed study:

Aim:	Problem Being Addressed	Beneficial Impact of the Research
1	Limited data exists on clinically relevant determinants of sleep quality and SDB in persons with SCI. Very little is known about sleep quality and prevalence of sleep disorders in racially diverse persons with SCI.	a) The research will quantify sleep quality, mood, pain, and presence of risks for SDB and insomnia in SCI participants using state-of-science evaluation techniques and validated instruments. b) The research brings needed attention to the problem of poor sleep quality and SDB after SCI, particularly among underserved ethnically diverse persons (Hispanic and Black). c) In addition to questionnaires, sleep studies will be conducted using the gold standard of clinical polysomnography, which will provide the most discriminating evidence for diagnosis of SDB. d) A prevalent diagnosis of SDB will justify vigilance from health care providers in anticipating the risk, and provide treatment of this disorder. e) The research will develop a rich database of sleep disorders and clinical outcomes in minorities and underserved SCI participants.
1	Cognitive deficits in SCI impair rehabilitation and long term social re-adaptation and vocational pursuits. SDB in general, has been associated with impairments in memory, attention, and executive	a) The research will identify the association between SDB and cognitive impairments in SCI by using a battery of well-defined neuro-psychological tests and comparing

	function. These deficits are important for day to day activities. **SCI participants with SDB may indeed demonstrate worse cognitive impairment in these domains**. More study is needed to determine the full extent of the interaction between SDB and SCI and their combined impact on cognitive function.	results between those with and without SDB. b) Additionally, other factors that may impact cognitive performance including pain severity, mood, pre-morbid intelligence, duration of injury, presence of insomnia, and use of sedating medications will be measured and included in a multivariable regression model to better delineate the impact of each of these factors and SDB on cognitive impairment.
1 and 2	Although there is now some data that demonstrate increased prevalence of poor sleep quality and SDB in SCI subjects, there is no clear evidence that treating these conditions will lead to short and long term benefits. PAP is a medically-justified intervention in persons with SDB, but has seen limited use in persons with SCI. Strength of evidence does not currently support screening for SDB and intervention with PAP in persons with SCI. Persons who are prescribed PAP are not always compliant with its use. Compliance in this population has seen limited study. The impact of PAP on cognitive outcomes in chronic SCI is unknown The impact of PAP on surrogate CV biomarkers, mood, and quality of life in this population is unknown.	a) The research will determine the effectiveness of PAP in treating SDB in chronic SCI using gold standard research methodology (RCT). b) The research will provide the empirical support necessary to justify treatment of SDB in persons with SCI. c) The research will examine population-specific compliance levels in PAP use, and identify whether compliance influences health-related outcomes. d) Our clinical trial will identify the impact of PAP therapy on cognitive measures, mood, quality of life, and surrogate CV endpoints. All these measures are relevant to the emotional and physical well-being of participants with chronic SCI and will likely have a practical impact on day to day living in this population.

Objectives/Specific Aims/Hypotheses

The proposal describes a multi-center double blinded, placebo controlled randomized trial (RCT) designed to examine the impact of SDB treatment in persons with chronic SCI. The **central hypothesis** is that the treatment of SDB with PAP will improve cognition, sleep quality, HRQOL, and CVD surrogate measures in persons with chronic SCI. The specific aims and hypotheses of the proposed research are:

Specific Aim 1	**Determine the associations between sleep disordered breathing (SDB) and cognitive impairments in chronic SCI and the impact of PAP therapy on cognitive measures in a cohort with chronic SCI and SDB.** *Hypothesis 1a:* Compared with patients without SDB, patients with SDB will exhibit more severe and widespread cognitive impairments (in memory, attention, and executive function), while controlling for depression, pain severity, duration of injury, level of injury, sedative use, and pre-morbid intelligence *Hypothesis 1b:* SCI participants who are randomized to four months of therapeutic PAP will show improvement in cognitive measures (memory, attention, and executive function) compared with those receiving sham PAP.
Specific Aim 2	**Determine the impact of PAP therapy on surrogate CV biomarkers, sleep quality, quality of life, mood, and pain in a cohort with chronic SCI and SDB.** *Hypothesis 2a:* SCI participants randomized to four months of PAP will show an improvement in CV biomarkers (hs-CRP, TNF-a, VCAM-1, adiponectin, and 8-isoprostane) compared with sham PAP. *Hypothesis 2b:* Sleep quality, quality of life, mood, and pain will improve in SCI participants receiving PAP and stay the same or worsen in those randomized to sham PAP.

Research Strategy and Study Design

Study Overview:

During the 4-year study period we will screen 200 SCI participants who meet eligibility criteria and consent to participate with portable level II polysomnography (PSG) and randomize 100 subjects who have SDB to auto-PAP or sham PAP. Participants will be recruited from the University of Miami (Miami Project to Cure Paralysis), the Miami VA, Wayne State University (Michigan Rehabilitation Institute), and affiliated Detroit VA through their outpatient SCI clinics and/or inpatient rehabilitation units. Participants will be asked to complete questionnaires measuring sleep quality (SQ), SDB risk, insomnia severity, daytime sleepiness, pain severity, mood, and HRQOL. They will undergo an overnight, at home (or if hospitalized, in the hospital room) portable unattended PSG performed at their normal sleep time. Subjects with an apnea-hypopnea index (AHI) ≥ 10 events/hr will be randomized to receive 4 months of auto-PAP therapy or PAP set at a fixed pressure of 3 cmH20 (sham PAP).

We will perform neuro-psychological evaluations prior to randomization on all participants who complete a portable PSG to evaluate general and pre-morbid function, immediate verbal memory, simple and sustained attention, processing speed, and executive function. Selection of these particular cognitive measures reflects impairments in these domains observed in patients with SDB within the general population.[14,30,32,76] These domains are also impaired in patients with acute and chronic SCI.[6-8,77,78] **Importantly, none of the cited SCI studies have examined the potential role of SDB in cognitive impairment in SCI participants.**

One cognitive measure (PASAT) and 3 sleep questionnaires (PSQI, FOSQ and ESS) will be repeated at 1 month follow-up in those randomized to therapy or placebo. Complete neuro-psychological evaluations will be repeated at the 4 month follow-up time point in those with SDB who were randomized to PAP or sham PAP (primary outcomes). All measures obtained from these repeated assessments will be subject to a Reliable Change Index analysis to control for potential practice effects.[79] We will obtain blood and urine samples for measurement of CV biomarkers at time of randomization and the four month follow-up. Additionally, sleep and quality of life questionnaires will be repeated at four month follow-up (secondary outcomes).

Study Population:

We will perform unattended portable level II PSG on SCI participants from the Miami and Detroit study sites (100 from each site) who meet the following eligibility criteria:

Inclusion Criteria:

- Chronic tetraplegia or paraplegia (C4-L1), American Spinal Injury Association (ASIA) Impairment Scale A, B, C and D
- 18 years and older
- At least one year post injury
- Hearing and vision suitable for comprehension of instructions, and perception of cognitive test stimuli
- No color blindness as measured by a brief screen with color perception Ishihara cards
- Stable medical condition for 2 weeks prior to enrollment. Patients admitted to hospital will be eligible for enrolment if the acute illness precipitating admission is in recovery phase for 2 weeks or longer

Exclusion Criteria:

- Diagnosis of SDB and successful positive airway pressure (PAP) therapy prior to injury. Those with a diagnosis of SDB post injury who are not receiving therapy for SDB (PAP, surgical, and/or oral appliance) are eligible for study enrollment
- Patients who are intubated, have a tracheostomy, and/or are using long term invasive/non-invasive positive pressure ventilation
- Participants with predominant central sleep apnea on PSG requiring bi-level PAP therapy
- Severe traumatic brain injury (GCS < 8 at first assessment)
- Unable to understand or read English at a grade 5 level
- Inability to provide informed consent
- Evidence of advanced neurological or systemic disease that may affect cognitive functioning (e.g., Alzheimer's disease, Dementia, Parkinson's disease)
- Significant aphasia or language impairments

Randomization Protocol

Participants who meet above eligibility criteria and are diagnosed with SDB with AHI ≥ 10 will be randomized to treatment with either auto-PAP or fixed PAP set at 3 cmH20 (sham PAP). It is anticipated that 100 participants will have AHI ≥ 10 (50 from each site) and undergo randomization to treatment or placebo in a 1:1 ratio within each center.

The randomization sequence will be generated by the study statistician using a computer-generated random-number table. The randomization numbers will be placed in serially numbered, sealed, opaque envelopes available to the study PI/site PI. The study coordinator from each site will request an envelope to be opened by the PI at the time of randomization. The study coordinator and the participants will be blinded to treatment assignment. Interpretation of study results will occur blind to study arm assignment.

Intervention

All randomized subjects will be fitted with a nasal or full-face mask and head gear. PAP will be delivered by an auto-titrating device (Resmed S9-Autoset, San Diego USA). These devices automatically set the level of delivered pressure to ensure upper airway patency, to treat detected apneas and hypopneas, thereby eliminating the need for a pressure titration sleep study to be performed in the sleep laboratory. Auto-PAP has been successfully used in several patient populations and may improve compliance with PAP. [80-83] Participants who are randomized to the placebo arm will receive an auto-PAP device that is set to a fixed low pressure of 3 cmH20 without an ability to titrate according to detected respiratory events. The pressure is too low to eliminate respiratory events and serves as sham or sub-therapeutic PAP (placebo PAP). Additionally, six extra

4 mm holes will be cut in the rubber collar of the connecting tubing at the mask end. These extra blow-off holes, together with the standard hole in the PAP mask, allow more air to escape and keep the nasal pressure low while ensuring no CO2 re-inhalation. This method has been successfully and safely used as a placebo in previous RCTs in participants with SDB.[60,84,85]

The auto-PAP machines will record the number and type of respiratory events detected, the pressure delivered in response to these events and the amount of time that the machine was on and delivering pressure to a patient. All subjects will be instructed to use the device nightly during sleep, for the ensuing four months. Objective compliance checks will be conducted at 1 week, 1 month, and study completion, by having the subject present the PAP "Smartcard" for download and interpretation. To increase patient compliance and decrease variance in outcomes introduced from differing degrees of exposure to the intervention, we will employ standardized procedures for management of PAP currently employed at University of Miami PAP clinic. These include instructing subjects on machine and mask use and regular phone follow-up for troubleshooting as necessary. The study PI will review compliance downloads and instruct the Research Associates (RA) to contact participants if compliance is low or machine reported air leakage from mask is too high. This is will be done for both arms of the study. The RA will not be aware of the details of the compliance report or machine pressure delivered to maintain blinding. Daily compliance will be reported as the total number of hours of PAP use per 24 hour period. Patients who use PAP > 4 hours/night for more than 50% of the nights at 4 month follow-up will be classified as PAP compliant.

Baseline Measurements All Subjects: At the Miami and Detroit sites the study RA will approach SCI individuals identified by the study PI and Co-investigators to determine eligibility for participation in the study. Upon consent, we will ask participants to complete several questionnaires detailed below. We will schedule participants for a single night unattended portable home PSG within one week of enrollment to evaluate sleep architecture and diagnose SDB. The RA at each site will review medical records to document medical and psychological co-morbidities, medication use, laboratory data, spinal cord injury level, ASIA classification, and duration of injury. We will interview participants during their enrollment visit to obtain a medical/sleep history, and anthropometric measures (height, weight, neck circumference, and abdominal girth at end expiration). Whenever possible the RA or PI/site PI will complete the international SCI core dataset for each participant.[86,87] Additionally, we will use the international SCI CV function basic data set to obtain information about CV co-morbidity.[88] Cognitive testing will be completed at baseline on all subjects who complete portable PSG. **Figure 2 outlines study flow and measurements**.

We will obtain the following respiratory measures during PSG: a) AHI: defined as the number of apneas and hypopneas per hour of sleep, b) arousal index (AI): the number of arousals per hour of sleep, c) percentage of total sleep time (TST) spent with arterial oxygen saturation (Sa-O2) < 90%, d) mean minimum Sa-O2, and e) oxygen desaturation index 4% (ODI4), defined as the number of four percent desaturation events per hour of study time. Respiratory and sleep architecture definitions will be scored according to accepted criteria put forth by the American Academy of Sleep Medicine (AASM).[89] We will define SDB as an AHI ≥ 10. We will score hypopneas initially using alternative rules (>50% reduction in airflow with 3% desaturation or arousal). We will rescore using recommended rules (>30% reduction in airflow with 4% desaturation). In the sleep research community, there is currently no clear consensus on which scoring method is preferred. SDB prevalence rates reported in the literature differ depending on the definition used.[90] Consequently, we will perform all analyses with both definitions in mind and report any differences in observed associations.

Questionnaires:
All participants will be asked to complete questionnaires described below. Questionnaires are validated and have been used successfully in prior SCI and SDB research. The RA will hand out the

questionnaires and allow the participant to complete them in a private setting. The RA will be available to answer any questions that may arise and will check the returned questionnaires for completeness. All questionnaires are found in Appendix 10.

Sleep Questionnaires

1) Sleep Quality (SQ): We will assess sleep quality using the Pittsburgh Sleep Quality Index (PSQI).[91] The PSQI is the most widely used global sleep assessment tool. Validity and test-retest reliability of this instrument has been extensively studied. A global PSQI score greater than 5 yields a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa = 0.75, $p < 0.001$) in distinguishing 'good' and 'poor' sleepers.[92,93]

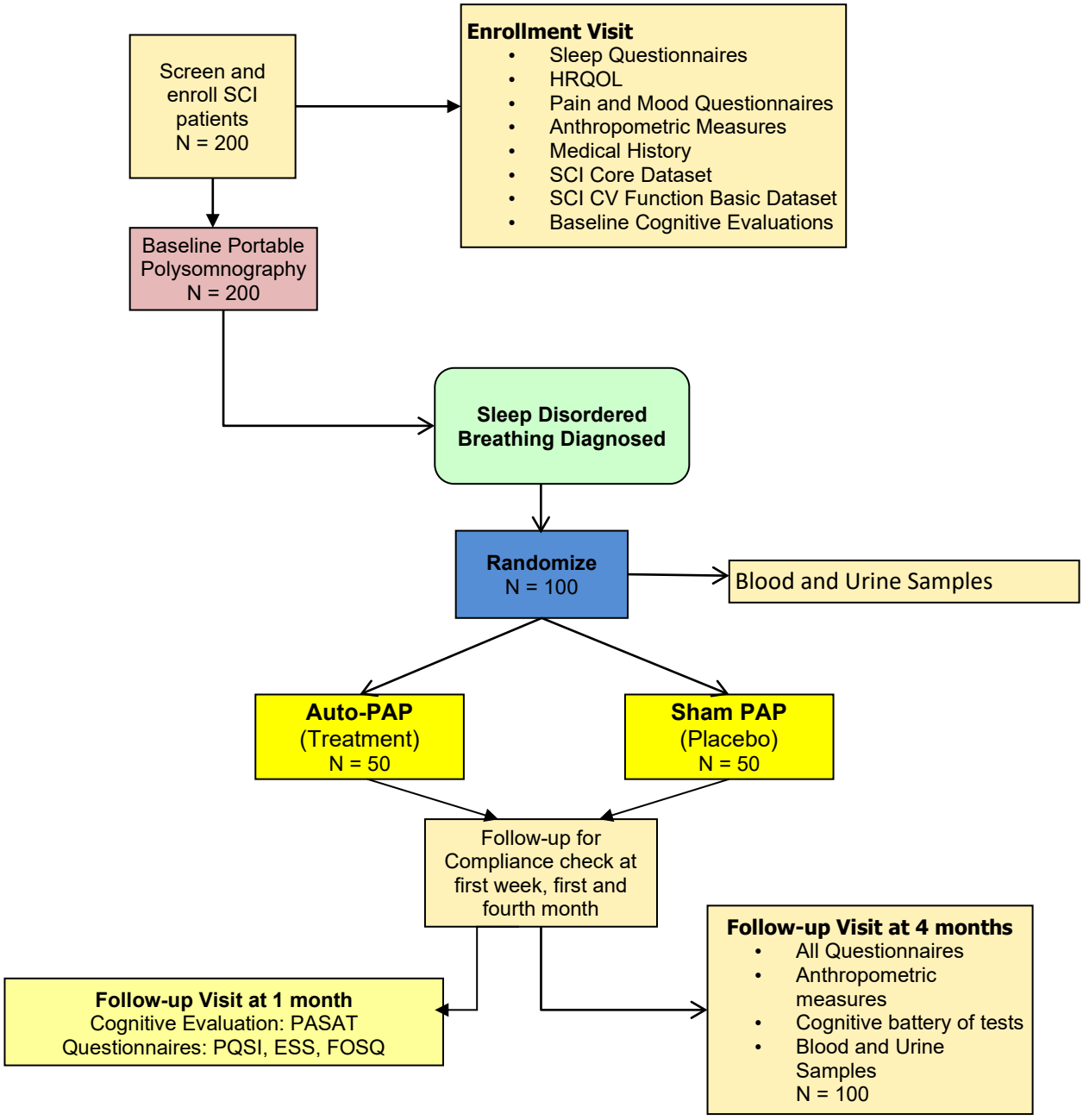
2) Chronic Insomnia: We will use the Athens Insomnia Scale (AIS) to assess insomnia in the study population. It consists of eight items: the first five pertain to sleep induction, awakenings during the night, final awakening, total sleep duration, and sleep quality; while the last three items refer to well-being, functioning capacity, and sleepiness during the day. Reliability and validity for the instrument have been well documented. [94,95]

3) Screening for SDB: We will screen for increased risk of SDB using the Berlin questionnaire (BQ). This is a validated questionnaire with good performance characteristics in the general population.[96] It has been successfully used by our group in the SCI population (see preliminary data).

4) Daytime Sleepiness: Epworth Sleepiness Score (ESS) is a valid measure of subjective daytime sleepiness.[97] Eight items are rated on a scale of 0–3, total scores range 0–24, with higher scores indicating a greater propensity to fall asleep in different situations. In samples of sleep apnea patients, it shows high internal consistency and correlates well with objective measures of sleep latency.[98-100]It has successfully been used in SCI individuals.[22]

5) Impact of Sleepiness on Functioning: The Functional Outcomes of Sleep Questionnaire (FOSQ) is the gold-standard, disease specific instrument designed to assess the impact of sleepiness on the ability to conduct daily activities. [101] The FOSQ has proven validity and reliability, and is sensitive to treatment changes. [102,103] There are 30 items, which are divided into 5 scales: Activity, Vigilance, General Productivity, Social Outcome, and Intimacy and Sexual Relationships. These scales are summed to make a total score. Higher scores on the FOSQ indicate self-perceived better daily functioning. The FOSQ has been used by our team in a previous study of acute SCI and sleep disorders.[23]

Figure 2. Study Flow and Measurements



Mood, Pain, and Quality of Life Questionnaires

1) Health related quality of life (HRQOL): We will measure HRQOL in participants using the Medical Outcomes Study Short Form SF-36 (v2, Quality Metric, Inc.).[104] We will score tests online, and express results as the coalesced scores for physical and mental domains. The SF-36 is the most widely used of the HRQOL instruments, and has been used in populations of persons with SCI[105-108], and those with a wide range of sleep disorders.[109-112] The instrument tests 8 coalesced dimensions of health that create a physical component score and a mental component score. Additionally, we will

use the recently proposed International SCI Quality of Life (QoL) Basic data set to facilitate future comparisons to other QoL studies in SCI worldwide. The QoL data set consists of 3 variables: ratings of satisfaction with general quality of life, satisfaction with physical health, and satisfaction with psychological health. All variables are rated on a scale ranging from 0 (completely dissatisfied) to 10 (completely satisfied).[113]
2) Depression and Anxiety: A) Beck Depression Inventory-2nd edition (BDI-II): is a brief psychological screening tool to assess depressive symptomatology. The BDI-II[114,115] is a 21-item, self-report measure with high test–retest reliability and internal consistency in a variety of patient groups, including those with SCI.[116] It has been shown to correlate with biological markers of depression and to be sensitive to change. B) State-Trait Anxiety Inventory (STAI): The State-Trait Anxiety Inventory is a well-validated and reliable instrument that has been successfully used with SCI populations to evaluate anxiety.[117-119]
3) Assessment of Pain: Presence and severity of pain will be determined by the *International Spinal Cord Injury Basic Pain Data Set (ISCIBPDS)* recently validated in persons with SCI.[120,121] Additionally, in accordance with IMPACT II consensus recommendations for evaluating pain outcomes in clinical studies, [122] we will determine the presence and severity of pain by a written numerical scale. Ranging from 0 to 10, with 0 meaning 'No pain' and 10 meaning 'Pain as bad as you can imagine,' the scale will be accompanied by the instructions, "Please rate your pain by indicating the number that best describes your pain on average in the last week." We will also use a verbal rating scale to measure pain intensity over the preceding week (none, mild, moderate, severe) as a secondary pain outcome measure.

Polysomnography: We will conduct portable in home Level II PSG in accordance with standards established by the AASM [123]. We will use the *Embletta x100* portable recording unit. The PSG recording montage consists of two electroencephalographic channels (EEG-C3 and C4), left or right electroculogram (EOG), chin muscle electromyogram (EMG), nasal cannula (NP-measure of airflow), thoracic and abdominal respiratory effort bands, body-position sensor, and pulse oximetry. The trained RA will connect participants to the device in the outpatient clinic or inpatient room. The *Embletta x100* will record overnight events. We will teach the participant and/or caregiver how to disconnect from the device prior to returning it to the clinic the following day. Portable sleep studies have been successfully used in outpatient clinical and research settings.[123-125] The *Embletta x100* unit has been validated against a standard in laboratory, attended PSG with good performance characteristics and accuracy in detecting SDB.[126]

A certified sleep technologist will perform manual scoring using 30 second epochs and standardized scoring techniques recommended by AASM.[89] Drs. Shafazand and Wallace will review all scored epochs and interpret the overall sleep study. PSGs performed by Detroit sites will be scored and interpreted centrally in Miami.

Specific Aim 1: Determine the associations between sleep disordered breathing (SDB) and cognitive impairments in chronic SCI and the impact of PAP therapy on cognitive measures in a cohort with chronic SCI and SDB.

Protocol: Dr. Johnson-Greene will train RAs at both sites to perform a battery of comprehensive, cognitive assessments to obtain a global evaluation of cognitive functioning in all subjects with SCI who undergo PSG. The particular emphasis is on measures related to cognitive impairment common in persons with SDB.[30] Administration of these tests by appropriately trained RAs is consistent with current standards of practice in clinical neuropsychology.[127] Sample protocol sheets and stimuli for each cognitive measure can be found in Appendix 10.

1) Pre-morbid Functioning:

WIDE RANGE ACHIEVEMENT TEST – IV (READING SUBTEST)[128]: The WRAT-IV Reading Subtest is a norm-referenced test that measures the basic academic skill of word reading. It was standardized on a representative national sample of over 3,000 individuals ranging in age from 5 to 94 years. Higher scores are indicative of better sight reading abilities and can serve as a proxy for pre-morbid intellectual functioning.

2) Simple and Divided Attention:
a) DIGIT SPAN SUBTEST OF THE WECHSLER ADULT INTELLIGENCE SCALE –IV[129]: The digit span subtest requires the individual to repeat a series of numbers in the same order, or in reverse order, than orally provided by the test administrator. Low scores on the digit span subtest suggest limited attention, while higher scores indicate a greater ability to concentrate and attend to orally presented information.

b) PACED SERIAL ADDITION TEST (PASAT): The PASAT measures divided, attention and working memory; cognitive domains that have been shown to be particularly salient to SDB. The individual being tested is given single digits at fixed intervals administered by a computer, and needs to add the current number to the last number on each successive presentation. The participant provides verbal responses and the examiner records the responses on a scoring sheet. Lower scores indicate greater impairment of attention. [130-132] **The PASAT is the primary outcome measure for this study.**

3) Processing Speed:
SYMBOL DIGIT MODALITIES TEST (SDMT)[133]: The SDMT is a substitution task that requires the individual being evaluated to replace symbols with the numbers assigned to them on a reference key. A time limit is imposed to complete the task. Only the oral version of the SDMT will be administered requiring verbal responses. The SDMT has shown excellent reliability, sensitivity, and validity.[134-136]

4) Memory:
HOPKINS VERBAL LEARNING TEST-REVISED (HVLT-R): The HVLT-R is an assessment of verbal learning and memory, composed of three learning trials, a delayed recall trial, and a delayed recognition trial. It has high test-retest reliability and validity, and has been used in studies of participants with chronic medical conditions. [137,138]

5) Executive Function:
WISCONSIN CARD SORTING TEST-64 (WCST): The WCST-64 is used primarily to assess perseveration and abstract thinking. It is considered a measure of executive function because of its reported sensitivity to frontal lobe dysfunction. As such, the WCST allows the clinician to assess strategic planning, organized searching, and the ability to utilize environmental feedback to shift cognitive sets and direct behavior toward achieving a goal.[139] The test is administered by computer. Participants will indicate their response verbally and the examiner will select the appropriate choice on the computer so that motor responses are not required.

This battery of tests takes approximately 75 minutes for subjects to complete. All cognitive measures will be completed at baseline and four month follow-up. Scoring of cognitive measures from Miami and Detroit sites will be completed by Dr. Johnson-Greene at Miami site who will be blinded to study arm assignment.

Specific Aim 2: Determine the impact of PAP therapy on surrogate CV biomarkers, sleep quality, quality of life, mood, and pain in a cohort with chronic SCI and SDB.

Given the increased prevalence of CVD and its associated morbidity, mortality and health costs in the SCI population[4,5], much attention has been paid in recent years to identifying and modifying traditional and nontraditional CVD risk factors in SCI. SDB is likely to be a nontraditional, but

modifiable risk factor. **Our study will be the first to evaluate in persons with chronic SCI, the association between SDB and surrogate cardiovascular biomarkers and the impact of PAP therapy on these measures.**

Biomarkers

We will measure inflammatory cytokines (TNF-α and hs-CRP), a cellular adhesion molecule (VCAM-1), a marker of oxidative stress (urinary 8-isoprostane), and adiponectin at baseline prior to PAP intervention and at four month follow-up.

Blood collection and sample preparation

Participants will be instructed to refrain from caffeine and alcohol intake for 24 hours before testing. Antecubital venous blood samples will be taken under antiseptic conditions in the post-absorptive state after an overnight (10h) fast, and will be drawn between 8:00 and 10:00 am. Ten milliliters of fasting blood will be obtained in EDTA-containing vaccutainer tubes or clot lysis activator tubes and centrifuged for 20 minutes at 1200 x g to obtain platelet poor plasma or serum, respectively.

After centrifugation, the serum or plasma are transferred to a new labeled tube and kept on ice or at 4°C until aliquots are prepared for storage. If multiple tubes are needed to obtain the requisite volume of sample, then samples from individual tubes will be pooled prior to preparation of sample aliquots. For freezing, aliquots of serum, plasma or urine will be added to appropriately labeled and identified cryogenic vials suitable for storage at ultra-low temperatures on the day of sample collection. Tube size will be dictated by the required sample volume. Sample vials will be placed in containers and frozen at ≤ -70°C until shipped to the laboratory for analysis. Samples to be shipped frozen will be placed in approved Styrofoam shipping containers containing sufficient quantities of dry ice to maintain samples in a frozen state for at least 48 hours and sent by overnight courier.

Urine Collection

First morning urine specimens will be collected at home by participants. Participants will be instructed to collect as much as possible of first morning urine into the supplied container, place the lid on the container carefully and tightly and bring the specimen as soon as possible on the same day to the RA. For those participants who self-catheterize, urine specimens can be collected from catheters (e.g. Foley catheter) using a syringe, followed by transfer to a specimen tube or cup. We will normalize urinary 8-isoprostane measurements to urinary creatinine levels to account for differences in dilution.

Biochemical Assays

Quality control procedures: For all quantitative metabolic and biomarker measures, the laboratory follows guidelines established by the Clinical Laboratory Improvement Act (CLIA) for quality control and proficiency testing. Each assay run must meet established quality control guidelines before results are accepted and reported. Sufficient stocks of control lots are maintained for long-term monitoring of assay precision and monitoring of long-term drift.

Clinical Laboratory and Biomarker Testing: Chemistry and immunoelectro-chemiluminescence (IECL) assays are performed by automated analyzer on a Roche Cobas 6000 analyzer following all manufacturer's instructions for instrument maintenance and assay calibration and test procedures. ELISA testing is performed by manual methods.

Assays, methodology, intra-assay CV (coefficient of variability), sample type and minimal sample requirements are shown in Table 1.

Table 1: Assay method, sample type and volume requirement by test

Test	Methodology	Assay CV	Reagent Manufacturer	Sample Requirement
C-reactive Protein	IECL	2.3%	Roche	0.3 ml Serum
Adiponectin	ELISA	4.7%	Mercodia	0.1 ml Serum
soluble VCAM	ELISA	5.8%	R&D Systems	0.2 ml EDTA Plamsa
TNF-alpha (high sensitivity)	ELISA	6.2%	R&D Systems	0.5ml EDTA Plasma
Urinary 8-isoprostane	ELISA	6.9%	Northwest Life Science Specialties	0.5 ml First Void Urine
Urine Creatinine (to normalize 8-Isoprostane)	Chemistry	2.1%	Roche	0.5 ml First Void Urine

Sleep, Quality of Life, and Mood

Sleep quality, quality of life, mood and pain will be evaluated at baseline and four months follow-up in each study arm using questionnaires, according to methodology described above.

Data Analysis:

Feasibility: The SCI Service at Miami VA actively serves approximately 300 patients. The Miami Project maintains a database of persons who have volunteered their participation in research studies and a database of individuals who have participated in past studies and volunteered additional participation. The database currently contains 3400 persons whose ages and levels of injury match the sought study participants. The Detroit VA SCI service oversees the care of greater than 100 patients/year. The Rehabilitation Institute of Michigan provides care for 350 SCI individuals. We anticipate completion of enrollment by the second quarter of Year 4, with 100 patients enrolled for PSG from each site.

Sample size justification and power: We will recruit 200 participants who meet our eligibility criteria and anticipate an SDB prevalence of 0.50 in SCI participants. This will allow us to randomize 100 participants with SDB to PAP or placebo arm. The neurocognitive test best characterized in both SCI and SDB is the Paced Serial Addition Test (PASAT).[35] The PASAT is our primary study outcome. A mean difference in PASAT scores of 7 discriminates between those with and without cognitive impairment in populations with and without SDB.[131] Assuming a standard deviation of 9 [131] and alpha of 0.05, a sample size of 40 per study arm has a power of 0.93 to detect a mean difference of 7 units. Assuming a PAP non-adherence rate and/or loss to follow-up of 40%, we will continue to have sufficient power (81%) to detect such a difference with our proposed sample size of 100.These findings would be in keeping with PASAT values obtained in non-disabled patients with SDB vs. controls [131], and PASAT performance in other populations (e.g. multiple sclerosis, mild traumatic brain injury) [132].

Planned analyses: We will score questionnaires while blind to PSG data and group allocation using instructions provided by the questionnaire developer. We will first examine continuous variables for normality. For those variables without a normal distribution, we will explore appropriate transformations in an attempt to achieve normality. Continuous variables will be summarized as means and SD, and categorical variables will be summarized as frequencies. Prevalence of poor SQ will be calculated as the proportion of individuals who complete the PSQI with a score of ≥ 5.

Prevalence of insomnia will be calculated as the proportion of individuals who complete the AIS with a score ≥ 6. Prevalence of SDB will be calculated as the proportion of individuals who undergo PSG with AHI ≥ 10/hr.

To determine baseline associations between SDB and cognitive measures (Hypothesis 1a), we will develop Generalized linear models (GLM), with each of the cognitive variables as dependent variables and presence or absence of SDB as an independent variable. The analyses will be repeated with AHI or ODI4 (measures of SDB severity) as independent variables. We will control for other co-variates including age, depression, anxiety, HRQOL, pain severity, duration of injury, level of injury, use of sedating medications, and presence of insomnia. For all GLM developed, the data may be transformed to meet the normality and homogeneity of variance assumptions of the analysis.

Primary Hypothesis (Specific aim 1, Hypothesis 1b)
A test of the primary null hypothesis, that PAP intervention does not increase mean PASAT score against the 1-sided alternative hypothesis that PAP intervention increases mean PASAT, will be based on a general linear model (GLM). PASAT score is modeled as a function of PAP intervention, using an indicator variable with 1 indicating PAP and 0 the sham treatment. A 1 degree of freedom test based on an F statistic will be used to test for a positive coefficient for the PAP indicator. This modeling approach provides a unified framework that accommodates covariates including use of sedating medications, years of education, level of injury, duration of injury, pain severity, presence of anxiety or depression, compliance with PAP, and recruitment center, each of which may reasonably be anticipated to influence PASAT score. We plan to include these covariates in our primary hypothesis test, which will be carried out at $\alpha = 0.05$. If the null hypothesis of no effect is rejected, computation of 95% confidence limits on the estimate of treatment difference in PASAT score mean will be carried out.

Secondary Hypotheses
A second phase of analysis will focus on CV biomarkers and measures of sleep quality, quality of life, mood and pain. These analyses are considered exploratory in nature and hence will benefit from comparisons within as well as between groups.

For within group contrasts, initial observations serve as baseline for assessing the effect of treatment at 4 months. As in a classical paired design, inference focuses on the difference between baseline and 4 month observations. Hence, individuals serve as their own control for an effect of intervention. The null hypothesis that the baseline does not differ from the 4 month measurement is tested using statistical methods for a paired design. For normally distributed measurements, a paired t test will be used. For variables that depart from normality and cannot be transformed to approximate normality, a Wilcoxon signed rank test will be used.

Comparisons between PAP and sham treatment groups at 4 months will be made based on the linear model described above for the primary endpoint. In contrast to PASAT, however, tests for treatment group differences of CV biomarkers and measures of sleep quality, HRQOL, mood and pain will be 2-sided. Because the number of secondary hypotheses to be tested is potentially large, these tests will be considered exploratory in nature. Accordingly, control of the false positive inference rate for these tests will be carried out at the group level, as described below, rather than for the entire set of secondary analyses. Similar approach will be taken for the analyses of select measures at the one month time-point.

Control of False Positive Rate of Inference
The inference of primary interest in this study is the effect of treatment on PASAT score. Because the test for intervention on PASAT is considered pre-planned, it will be carried out at α-level 0.05. Similarly, tests for effects on groups of CV biomarkers, sleep, mood and quality-of-life measurements

are considered pre-planned in the sense that measurements in each group will be subjected to statistical testing regardless of test outcome for PASAT. Accordingly, tests for multiple measurements taken in each category of biomarkers will be carried out at α-levels below 0.05. This approach recognizes that multiple testing is involved within each biomarker category and adjusts the significance level for individual tests downward to control the false positive inference rate at the category level. We will apply a False Discovery Rate (FDR) criterion of 5% separately for each category, thereby acknowledging the substantial overall number of tests per category but preserving power to detect true effects for each type of biomarker.

Primary analyses will be conducted in accordance with the intention-to-treat principle. We will also repeat analyses using a per protocol viewpoint. We will use statistical software, SPSS for Windows version 19 for all analyses.

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