Does Treatment Of Sleep-Disordered Breathing Improve Functional Outcomes In SCI?

STUDY PROTOCOL

NCT02830074

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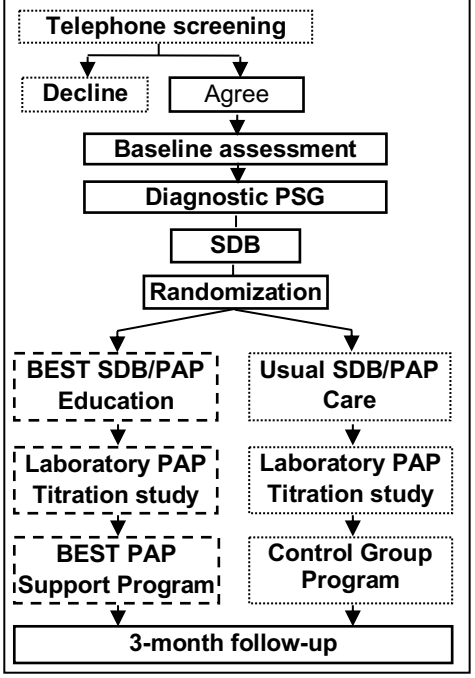
4. RESEARCH DESIGN AND METHODS

4.1. Basic Study Design (Figure 5):

Figure 5: Basic Study Design.



The proposed project is a 3.25-year double-blind randomized controlled trial (RCT) to test the efficacy of a comprehensive program to improve PAP adherance and sleep quality among Veterans with SCI/D and SDB. Participants will be enrolled from the JDDVAMC, the Ann Arbor VA (AAVA) and the Cleveland VA Medical Center (Cleveland VAMC). The approach to treatment will follow "best practice" models of care, including positive airway pressure (PAP) therapy, plus an established behavioral/educational intervention to improve acceptance and adherence to PAP and to improve sleep quality overall. A second component of the intervention will be 3 months of ongoing support for patients (and caregivers, if relevant) after the initiation of PAP treatment. This program will be compared to standard treament of SDB plus sleep education control condition used in our prior work.

Potential participants will be identified from among patients with SCI/D who receive care at the JDDVAMC, AAVA or Cleveland VAMC's SCI/D clinics. All will be mailed a letter describing the study and an "opt out" card. Those who do not "opt out", will be contacted by phone to complete a brief screening interview, and we will be invited to come to the JDDVAMC where written informed consent will be obtained [for those without use of upper extremities, we will use approved IRB procedures for consent (e.g., documented verbal consent, proxy consent from legal caregiver)], then a series of baseline assessments will be completed. The participant will then have in-lab PSG, including $P_{ET}CO_2$ monitoring. We anticipate enrolling up to 247 patients into the study, at least 74 of whom will be expected to have SDB and will continue on to randomization to intervention or control. Throughout the study, participants will be blinded to their group assignment, and observable aspects of the intervention will be "controlled for".

A PAP titration study (CPAP or BPAP) will be performed in those with SDB. On the day of that visit, they will be provided with the first component of the patient education program (designed for patients with SCI/D) as well. PAP treatment will utilize current clinical guidelines and best practices for the management of SDB.[43;54-56] subsequently, participants will receive weekly phone calls for 5 consecutive weeks, and will have ongoing support from the study interventionist for the first 3 months of treatment. At the end of that 3-month period, participants will be asked to return to the medical center and we will re-administer baseline questionnaires, as well as 1-month into treatment.

4.2. Setting:

Study activities will be carried out within the JDDVAMC in Detroit, MI, which is the home to a specially-equipped sleep research laboratory and a SCI/D clinic. The facility catchment area covers all of VA's VISN 11 (central Illinois, Indiana, Michigan and Northwest Ohio). At least 180 SCI/D patients are followed within this VA system. Participants will also be recruited from the AAVA, which has a sleep disorders clinic and SCI/D clinic (but no sleep laboratory), and the Cleveland VA. The AAVA follows at least 103 individuals with SCI/D annually, and refers patients to the JDDVAMC facility for laboratory sleep studies. Of the patients who receive care at the Cleveland VAMC's SCI Center, approximately 300 live within the study's catchment area.

4.3. Study participants: Recruitment, screening and enrollment:

To randomize a total of 62 Veterans in this study, we will reach out to all Veterans who receive SCI/D care at VAJDDMC, AAVA and Cleveland VAMC (**Table 1**, row A). We have developed close working relationships with the SCI/D teams at these sites, and we conduct clinical sleep evaluations for patients seen in the JDDVAMC and AAVA Centers. We will obtain updated lists of SCI/D patients quarterly from each site. We will begin recruitment at the JDDVAMC, followed by the AAVA 3 months later, and the Cleveland VAMC 3 months after that. Inclusion criteria are: adult patients with chronic SCI/D (>3 months post injury), American Spinal Injury Association (ASIA)[57] classification A-D (i.e., excluding those with no evidence of a neurologic deficit based on ASIA classification). Exclusion criteria are limited to: 1) receiving mechanical ventilation, 2) Only Current users with objective documentation of optimal compliance, 3) a clinical contra indication that prevents CPAP use , 4) recent health event that may affect sleep (e.g. CVA, acute MI, recent surgery or hospitalization), 5) Alcohol or

substance abuse (<90 days sobriety), 6) self-described as too ill to engage in study procedures, 7) unable to provide self-consent for participation (e.g., due to dementia). We will offer to re-contact patients 90 days after a health event or after 90 days of sobriety. Based on our current research program working with Veterans with SCI/D, we anticipate there will be a pool of at least 247 interested eligible individuals who consent to participate, and we expect that 27% of those enrolled will meet all study eligibility criteria (N=74). Our required sample size of N=62 is therefore feasible and realistic given the sampling frame and recruitment methods.

Table 1: Estimated recruitment, screening and participation rates.		**Percent (ratio)**	**Projected N**
A. Study recruitment sample (letter sent with "opt out")*			**N=591**
	Participant "opts out" of being contacted	15% (89/591)	
	Unable to contact by phone	10% (59/591)	
	Refuse telephone screening	3% (18/591)	
	Decline consent appointment	25% (148/591)	
	Decline participation at consent appointment	5% (30/591)	
	Eligible interested individuals (to be enrolled)	42% (247/591)	N=247
B. Enrolled participants			**N=247**
	Do not meet inclusion/exclusions (other than SDB)	10% (25/247)	
	Without SDB (AHI<5)	50% (123/247)	
	Refuse randomization (withdraw after baseline)	10% (25/247)	
	Eligible for randomization	27% (74/247)	N=74
C. Eligible for randomization			**N=74**
	Required study sample size**	81% (62/74)	N=62

*JDDVAMC (n=180), AAVA (n=111), Cleveland (n=300 w/in 2hrs of Detroit); **74=[required sample size for randomization (N=62)] + [19% margin (N=12)]. N=62 based on lower limit of 90% CI from preliminary data (Figure 2).

Percentages reflected in **Table 1** are based on our experience recruiting SCI/D patients into research studies. We recently sent recruitment letters to 92 SCI/D patients, and were able to screen 70 individuals by phone (76%). Among those patients, 26 (29%) did not meet the strict eligibility criteria for that study, and 15 (21%) were not interested in participating. This resulted in a consent rate of 32% of those who were sent initial recruitment letters. Given that the current study has fewer exclusion criteria (e.g., individuals will not be excluded based on medication use), we anticipate excluding substantially fewer patients at the screening phase. We conservatively estimate that enrolling 42% of individuals screened for the current trial. Furthermore, we have conservatively estimated that 50% of enrolled participants will have SDB, and will be eligible for randomization, although rates may be higher depending on level of injury (i.e., patients with cervical injuries have higher rates of SDB) and other SDB risk factors (e.g., use of narcotics).

Veterans will be sent a letter (IRB approved) and an "opt out" card that can be returned if they do not wish to be contacted. After 10 days, individuals who do not "opt out" will be contacted by phone and the screening questionnaire will be completed. The study will be explained, verbal consent for screening will be obtained and additional eligibility criteria will be assessed. To assess basic study eligibility, we will adapt a screening survey used in prior work with older Veterans with disabilities. The screening questionnaire includes information about basic inclusion/exclusion criteria (listed above) plus information about general sleep complaints.

Written informed consent will be obtained at the first in-person visit, prior to collection of research data. Capacity to give informed consent will be evaluated with a brief questionnaire (previously approved by our IRB) that asks the Veteran to recount major procedures and risks of the study. Veterans who are unable to provide informed consent will be excluded; proxy consent will not be pursued.

4.4. Procedures:

Once enrolled, participants will complete a baseline assessment at the sleep laboratory. All data will be collected by trained research personnel, using participant interview and monitoring in the sleep laboratory. Research staff will undergo structured training, including review of human subjects protection issues, emergency procedures, interviewing techniques, cultural sensitivity training, and in-depth instruction on data collection instruments and equipment. We have procedure manuals for all instruments and equipment to be used in this study. Adequate inter-rater reliability will be established and reassessed annually. The methods and instruments we have selected were chosen to minimize participant burden while maximizing reliability and validity. Whenever possible, we have used measures that have been studied in patients with SCI/D. As we have done in our preliminary studies, we will arrange for and provide transportation to the study site. Each participant will travel to the study site for 6 separate visits. The first two to gather baseline data, and the third to initiate the intervention

or control condition. The fourth and fifth visit will be to complete the 1-month and 3-month follow-up (**Table 2**). The final visit will be coordinated with participants to download their SD card at the 6 month mark from when they received the machine.

Table 2: Activities for each participant visit to the VAMC.

	Visit 1	Visit 2*	Visit 3	Visit 4	Visit 5	Visit 6
Screening and informed consent	✓					
Questionnaire assessments and respiratory measures	✓			✓	✓	
Attended polysomnography (PSG) or at-home sleep study*		✓				
PAP titration study (intervention begins)**			✓			
SD Card Download						✓

*During overnight sleep laboratory monitoring (7pm-7am) **only for those with SDB

4.4a. Baseline assessment: Once enrolled (after informed consent), a battery of questionnaires (**Table 6, below**) assessing sleep, quality of life and functional status will be completed in interview format. Participants will then return to the sleep laboratory for overnight attended, in-lab PSG and pulmonary function tests. An at-home sleep test will also be available to participants at their convenience.

Polysomnography. The technician will then apply PSG sensors (including measurement of end-tidal $P_{ET}CO_2$ to identify sleep-related hypoventilation), and the participant will be transferred into bed. The technician will observe the participant from an adjacent room, using closed circuit video, and will be immediately available for assistance. In the morning, spirometry and respiratory muscle forces will be repeated before the patient leaves the laboratory. The PSG recording will be scored by certified sleep technologists, using American Academy of Sleep Medicine (AASM) scoring criteria. Hypopnea will be defined as Scoring reliability will be verified by using the AASM scoring reliability testing every three months. Every record will be reviewed for scoring accuracy by Dr. Badr or Dr. Sankari or Dr. Salloum or Dr. Zeineddine. We anticipate that at least 68 individuals tested will have clinically diagnosed SDB based on PSG and will be eligible to move on to randomization to intervention versus control. Participants who agree to participate in baseline assessment will be compensated $50 for each night in the sleep laboratory and $50 for completing all questionnaires.

Pulmonary Function Testing. Immediately prior to habitual bedtime, the technician will perform baseline spirometry and measurement of respiratory muscle forces according to American Thoracic Society (ATS) 2005 criteria. Subjects will be tested in the seated and supine positions, with nose clips and mouthpiece, using the best values of three reproducible tests. The test will yield; the following measures: forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and FEV1/FVC ratio. Measurement of respiratory muscle forces will include Maximal Inspiratory Pressure (MIP) and Maximal Expiratory pressure (MEP). For MIP, the participant will be coached by a trained technician to perform a maximal expiration prior to inserting mouth piece and closing lips tightly around it, followed by a maximal inspiratory effort. Nose clips will be used utilized to prevent air leak. The most negative value of three individual maneuvers will be used as the MIP. For MEP, the participant will be coached by a trained technician to perform maximal inspiration prior to inserting mouth piece and closing lips tightly around it, followed by a maximal expiratory effort. The highest value of 3 individual maneuvers will be taken as the MEP.

4.4b. Randomization: Individuals who have SDB based on the diagnostic PSG will be randomly assigned to receive the BEST program or the control condition (See below) using a randomized block design based on level of injury (cervical or thoracic). Participants and research staff (except intervention staff) will be blinded to group assignment. It may be difficult to keep assessment research staff blinded to group assignment if participants inadvertently describe the intervention. Furthermore, assessment staff will be blinded to study research questions, and study documents (e.g., consent forms) will indicate we are comparing “two programs to help patients with SDB” and participants will be blinded to the content of the intervention program they do not receive. We have successfully achieved blinding of assessment staff in prior research by controlling for “observable” aspects of the intervention program (e.g. frequency of contacts). In this way, “double blinding” can be achieved in behavioral treatment trails. Randomization procedures will follow the CONSORT criteria for randomized trials.[58] Dr. Mitchell (statistician) will generate the randomization sequence for each block, and two sets of envelopes containing group assignment will be generated. The envelopes will be sealed and stored in the office of the study’s statistical clerk where the intervention and assessment staff will not have direct access. Only Drs.

Badr and Sankari and intervention staff will have access to the randomization envelopes. Once final eligibility is determined, the next envelope in the sequence for the appropriate block will be opened and that will determine the intervention group to which the participant is assigned. This will be communicated to the appropriate Research Staff.

4.4c. Best Practices, Education, Support and Training (BEST) Program for Veterans with SDB: We recently developed this 3-part program to address barriers to PAP acceptability and adherence identified in our pilot work. In total, the program will last 13 weeks (**Table 3**). The first aspect of the program will be to apply "Best practices" models of care to the PAP therapy itself, starting with an in-lab PAP titration study on night 1 of week 1. Second, an Educational component will be added based on a program developed and used by Dr. Martin at the VA Greater Los Angeles Healthcare System, which includes information about sleep apnea, patient decision making and motivational enhancement, PAP use and specific strategies to improve sleep quality among those with functional limitations. Dr. Fung has assisted in adapting aspects of this program for patients with disabilities. Third, we will provide ongoing Support during the first 3 months of PAP therapy and ongoing Training for the patient and caregiver (if the patient has a home caregiver and wishes him or her to be involved). This will include weekly phone calls from the study staff and the availability of a "hotline" to call if difficulties with the equipment arise. Weekly intervention notes will be maintained documenting the intervention process, including the involvement of caregivers in any of the study components (Described below). The study interventionist will prospectively monitor participant adherence using remote monitoring technology, which is available at the JDDVAMC. Dr. Martin will train the study interventionist in the use of the intervention, and will have weekly consultation meetings with the interventionist.

Table 3: Overview of the 13-week BEST Program.

Location	In-Lab		At-Home											
Week of Intervention	N1	1	2	3	4	5	6	7	8	9	10	11	12	13
PAP education program (with patient and caregiver)	✓													
PAP titration study (overnight stay in sleep laboratory)	✓													
Weekly PAP support visits and phone calls		✓	✓	✓	✓	✓								
Troubleshooting hotline		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Remote PAP Adherence monitoring		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

BEST Program Component 1: PAP Titration: Individuals with SDB will be informed of the results of their overnight study, and will be asked to return to the laboratory for a PAP titration study (CPAP or BPAP if needed). To improve PAP adherence, the visit will include individualized educational content, tailored for patients with SCI/D, including issues such as mobility/dexterity limitations that might affect acceptance of PAP. If the patient has a caregiver, s/he will also be provided with information and (if the patient agrees) will be able to participate in the educational component of the intervention. Prior studies have shown that, with the assistance of a caregiver, patients with dementia can successfully adapt to PAP, and we believe caregivers can play a critical role in the patient's adjustment to the use of PAP.[59] One week after the PAP titration study, the patient will be contacted by phone and additional support and troubleshooting will be provided. Studies show that follow-up within one week of PAP initiation increases adherence.[60-62] At the end of this session, the patient (and/or caregiver) will be provided with all written materials needed for the second component of the intervention. Given that most SCI/D patients depend upon the assistance of paid or informal family caregivers, with the patient's permission, this person will be engaged in the educational components of the intervention, and will be provided with information on how best to assist the patient.

BEST Program Component 2: Patient (and Caregiver) Education: This component of the intervention will involve adaptation of an OSA disease-specific intervention, which is based on the chronic disease management model using social cognitive theory and transtheoretical models of behavior change.[63;64] On the night before PAP titration, the patient will be provided with information on understanding OSA symptoms and consequences. The program will then continue with 3 additional telephone contacts, which are focused on setting goals for PAP use, preparing to troubleshoot possible difficulties with PAP, communicating with providers about PAP, and increasing the likelihood of sustained adherence by encouraging self-management. Components of the program will also address specific strategies for improving sleep quality, such as adjusting time in bed, setting a regular schedule, and limiting non-sleep activities in the bed. The participant's PAP use will be remotely monitored, and will be discussed with the participant during weekly calls (**Table 4**). A major focus of the program will involve troubleshooting commonly occurring problems with PAP, tailored to the participant's ongoing experience with

PAP, in addition to understanding how specific aspects of an individual's use of PAP relates to the management of his/her OSA and targeted outcomes.

Table 4: BEST PAP Education Program components by week of intervention

Week (Format) Topic	**Components**	**Adaptations for SCI/D**
Week 1 (Face-to-face at PAP titration visit) "Understanding SDB and PAP"	· What is SDB? · How does PAP work? · AHI with and without PAP · Symptoms that may be PAP responsive · Application and cleaning of equipment · Sleep education/healthy sleep habits · Set consistent bedtime/rise time	· Symptoms common in SCI/D (e.g. fatigue, lethargy) · Adaptation for mobility and dexterity limitations · Caregiver considerations for transfer in/out of bed
Week 2 (Phone) "What are the risks of untreated sleep apnea?"	· Consequences of untreated SDB · Benefits of treating SDB in SCI/D · Review remote monitoring data · Set PAP use goals · Troubleshoot equipment challenges · Informed choices about PAP use · Adjust bedtime/rise time (if indicated)	· Benefits highlighted that impact SCI/D (improved sleep=improve functioning and QOL) · Strategies for coping with usability challenges that have arisen due to disabilities or limited mobility
Week 3 (Phone) "What are the benefits of treating sleep apnea?"	· Review remote monitoring data · PAP use goals, monitoring and troubleshooting · PAP specific cognitive strategies · Improving sleep quality with healthier sleep hygiene · Adjust bedtime/rise time (if indicated)	· Focus on issues related to limited physical activity · Identify maladaptive thoughts related to SDB and functional limitations
Week 4 (Phone) "Managing sleep apnea over the long-term"	· Review remote monitoring data · Long-term planning for PAP use: identify problems in advance · Maintaining good sleep quality over the long-term · Chronic disease management · Adjust bedtime/rise time (if indicated)	· Discuss issues related to maintaining use (e.g., follow-up visits in sleep clinic, supply replacement · Discuss handling issues of other symptoms (e.g., pain) that may temporarily disrupt sleep · Apply patient's effective SCI/D coping strategies to PAP
Week 5 (Phone) "More steps to sleep better"	· Review remote monitoring data · Set goals to adjust sleep schedule · Discuss PAP benefits · Discuss PAP inhibiting factors · Side effects · PAP machine problems · Factors that make sleep worse · Factors that make sleep better · Adjust bedtime/rise time (if indicated)	
Week 6 (Phone) "Maintaining what I've gained"	· Review remote monitoring data · Long-term planning for PAP use · Keys to sleep apnea self-management · Identifying triggers for non-use	

BEST Program Component 3: Ongoing PAP monitoring and supportive follow-up: The third and final component of the program will incorporate state-of-the art remote tele-monitoring of PAP using Encore Anywhere. This platform is routinely used in VA Sleep Disorders Centers. Dr. Martin's research group is currently using this technology in a study of older Veterans using PAP (VA HSRD IIR 12-353-2), and we have been able to obtain PAP data (or confirm non-use) in all study participants (n=52 to date). Participants will be provided with a model compatible with their PAP machine so that nightly use data will be available to the study interventionist each day. In the BEST group only, the interventionist will review remote monitoring data daily and will contact the participant if the PAP machine is not set up and transmitting data. Once the PAP machine has been set up, the interventionist will continue to review Encore Anywhere twice per week, and will initiate a phone call to the

participant if the device is used for <4 hours on 2 consecutive nights (or if data are not transmitted). In all instances the interventionist will work with the participant to set PAP use goals, and to troubleshoot any equipment-related issues. During each of the planned weekly phone calls, the interventionist will review the patient's PAP use information (by printing out and reviewing the Detailed Summary Report) to assist with setting goals. This report includes average and total use statistics for a variety of metrics as well as the residual AHI (i.e., severity of SDB while using PAP) and evidence of mask leak. This is a higher frequency of monitoring than what is recommended as part of routine care.

Control condition program: The control condition for this study is based upon the core components of control programs used in our prior work which are shown to be credible to participants, but not to lead to changes in sleep quality, PAP use or other study outcomes as described above. Participants in the control condition will receive non-directive, general information. The control intervention is described in **Table 5**.

Table 5: Attention Control Condition Non-directive Education Program

Week/Format	Title	Components/Topics
Week 1: Face-to-face	Understanding sleep	General information about sleep in adults
Week 2: Phone	What is sleep apnea?	Basic information about sleep disordered breathing
Week 3: Phone	Good sleep hygiene	Discuss sleep hygiene: no individualized recommendations
Week 5: Phone	More steps to sleep better	Discuss PAP benefits
Week 6: Phone	Maintaining what I've gained	Long-term planning for PAP use

Control Program Component 1: Standard diagnostic testing: The overnight PAP titration study will follow standard clinical guidelines as described above for BEST program participants; however, no additional patient education about PAP itself will be provided during this visit. Instead, general information about sleep in adults will be provided. This will account for the "extra" social contact associated with being in the study, but this type of information is not expected to change sleep quality or improve PAP acceptance or adherence.

Control Program Component 2: General sleep education: A non-directive general sleep education program will be delivered to individuals in the control program with 3 additional telephone contacts. The purpose of this component is to control for the added social contact of participation. The interventionist will not provide individualized recommendation and will give accurate, but non-directive, information about sleep apnea, sleep hygiene and sleep changes across the adult lifespan. We have used this control program in prior randomized controlled trials. Participants report that the program is "credible", but we have found virtually no effect on sleep quality metrics.

Control Program Component 3: PAP adherence monitoring: Information on PAP adherence will be monitored remotely as described above, but the interventionist will monitor and use this data differently. The interventionist will log into the Encore Anywhere system and verify that the PAP machine has been set up and is transmitting data. If this has not occurred within one week of the PAP titration study, the interventionist will address this during the second intervention session (by phone). The interventionists will assist with technical difficulties if the PAP machine has not begun to transmit data. The frequency of PAP adherence monitoring in the control group will be one week and monthly thereafter, which is consistent with the American Thoracic Society Recommendations related to PAP initiation in general.[65] The interventionist will call the patient and provide general information consistent with standard care (in the absence of a targeted PAP adherence program) for new PAP users.

Intervention process measures: There will be several measures of the intervention process monitored throughout the study. This will assist with subgroup analyses, and with better understanding how the BEST intervention is applied in the study, and therefore would be implemented in clinical care.

Caregiver support: The study interventionist in both groups will keep a weekly log in which all subject contact is documented (see Intervention Fidelity Monitoring, below). This will include documentation of involvement of caregivers in any interactions with participants. In the BEST group only, participants will be actively encouraged to solicit support from caregivers if their assistance is needed, and with the participant's permission, the interventionist will communicate directly with caregivers when needed.

Intervention Fidelity Monitoring: For each session of the BEST and Control programs, a checklist of topics covered will be used to document completion of each component of the session. In addition, the duration of each session, and whether the patient's caregiver was present (with the patient's permission) during the intervention session will be recorded. Throughout the intervention period in both groups, all telephone contacts will be

documented, and the total number of unscheduled calls will be computed. For telephone sessions, the interventionist will document whether the information was presented to the patient, caregiver, or both simultaneously. We have used this systematic checklist method our in prior research and have shown it correlates well with completion of the forms by an observer. While recording sessions and independently scoring them is more desirable, we have found that audio-recording is a barrier to participation in research for some Veterans, and we have therefore chosen to use this method instead. In addition, Ms. Bascom (BEST program) and Ms. Nickert (controls) will remain blinded to the content of the other intervention arm. This will also help to prevent "contamination" of the control group by components of the active treatment.

4.4d. Post-intervention follow-up assessment: Enrolled participants will be asked to return to the medical center and complete a post-intervention assessment (**Table 6**) three months after the beginning of PAP treatment. For those who are unable or unwilling to come to the facility, a research assistant will travel to their home and complete assessments at that location. If the individual lives more than 50 miles away or has relocated out of the area, the questionnaire data will be gathered over the telephone. We selected the 1-month and 3-month follow-up time frame as it strikes a balance between the desire to evaluate benefits of treatment while considering that longer follow-up intervals may decrease our ability to contact participants for re-assessment and that intervening health events may increase the variability in treatment response. Participants who complete the 3-month follow-up assessments will be compensated $50 for their travel and time.

Table 6: Study variables and measurements at each assessment visit

			Visit		
Descriptive and clinical measures		**Measurement Instrument**	Base-line	1m f/up	3m f/up
Age, race/ethnicity, marital status, educ.		Core demographics questionnaire	X		X
Self-reported comorbidities		Comorbidity Index[66]	X		X
Pain		Brief Pain Inventory[67]	X	X	X
PTSD symptoms		PC-PTSD[68]	X	X	X
Anxiety symptoms		Patient Health Questionnaire, GAD-7[69]	X	X	X
Sleep Measures		**Measurement Instrument**			
SDB severity (PSG)		Apnea/Hypopnea Index from PSG	X		
Symptoms of restless legs syndrome		RLS questionnaire	X		X
Insomnia symptom severity		Insomnia Severity Index (ISI)[72]	X	X	X
PAP equipment usability		USE-SA[70;71]		X	X
Main outcome measures	**Aim**	**Measurement Instrument**			
PAP adherence	1	Remote monitoring of nightly PAP use		X	X
Subjective Sleep Quality	1	Pittsburgh Sleep Quality Index (PSQI)[72]	X	X	X
Daily sleep diary	1	AASM Consensus Sleep Diary[73]	X	X	X
Quality of life	2	WHO-QOL BREF[74]	X	X	X
Functional Status	2	SCIM-SR[76]	X	X	X
Depressive symptom severity	2	PHQ-9[75]	X	X	X
Fatigue Symptoms	2	FFS[78]	X	X	X
		ESS	X	X	X
		CHART	X	X	X
Forced vital capacity (FVC)	2	Spirometry	X	X	X
Maximum inspiratory pressure (MIP)	2	Respiratory muscle force measures	X	X	X

Descriptive and Clinical Measures:

Demographic data, including age, gender, race/ethnicity, marital status, living situation, income, education, employment, and smoking history, will be used to describe the sample and to gather information on potentially relevant covariates and variables for subgroup analyses. Selected variables will be re-assessed at follow-up. The Comorbidity Index is a validated, self-report measure of physical and mental comorbidity. This 36-item questionnaire has a 30-item physical component and a 6-item mental component and was developed for Veterans. Higher scores indicate greater comorbidity. The total score will be used as an index of comorbidity burden.[66] The Brief Pain Inventory-Short Form[67] is a 9-item self-administered questionnaire that measures pain severity, pain treatments used, and daily interference of pain over the past week. The BPI has high construct validity and is well-correlated with other pain measures (r=.61-.74). Pain severity and interference scores will be used. The 4-item Primary Care PTSD Screen (PC-PTSD)[68] will be used to evaluate presence/absence of PTSD. The scale has a sensitivity of 0.78, and specificity of 0.87 compared to clinical diagnosis of PTSD in Veterans.

The Generalized Anxiety Disorder-7 (GAD-7)[69] is a component of the PRIME-MD that was developed for evaluation of Generalized Anxiety Disorder (GAD). This 7-item scale has sensitivity and specificity above 0.80 for GAD, panic disorder, social anxiety and PTSD. The GAD-7 total score will be used to measure anxiety symptoms. Pulmonary Function Testing will include spirometry and respiratory muscle forces, in the upright and supine positions. Forced vital capacity (FVC) in the supine position will be the primary measurement since the majority of patients sleep in the supine position.

Sleep Measures:

Laboratory Polysomnography (PSG): Participants will be studied in our specially-equipped sleep laboratory at the JDDVAMC using a wireless PSG system (**Figure 1**, above). The recording will include a standard clinical PSG montage, including EEG, EOG and EMG for sleep staging, and respiratory effort and airflow for evaluation of sleep disordered breathing. In addition, end tidal PCO_2 ($P_{ET}CO_2$) will be measured to identify hypoventilation during sleep. Sleep parameters will be recorded continuously from bedtime to rise time on the night of PSG. Sleep and respiration will be scored using standard AASM criteria.[76] The Apnea Hypopnea Index (AHI) will be computed as the number of apneas + hypopneas per hour of sleep. Sleep disordered breathing will be defined by an AHI≥5 events per hour of recorded sleep, using the AASM's standard scoring criteria.

Sleep Questionnaires: We will use the Insomnia Severity Index (ISI)[72] to assess insomnia symptoms. The ISI is a 7-item instrument using Likert-type scales that measure perceived severity of insomnia symptoms from 0 (not at all) to 4 (very much). The ISI correlates well with the PSQI (r=.67), and sleep diary measures (r's=.32-.91). The Usability of Sleep Apnea Equipment-P (USE-SA(P) version 3.0) will be used to assess PAP usability at the 3-month follow-up. The self-administered questionnaire contains 18 items that measure 5 aspects of PAP equipment usability, including learnability, memorability, efficiency, device feedback, and satisfaction. An additional 7 items assess the frequency of usability issues, and 3 items ask about equipment features.[70;71]

Main Outcome Measures:

The Pittsburgh Sleep Quality Index (PSQI)[72] is an 18-item questionnaire that assesses sleep quality and disturbances over the past month. The PSQI is sensitive for distinguishing normal and abnormal sleepers and has good test-retest reliability. We will use the 3-factor scoring, which has been shown to have superior psychometric properties compared to the original 7-factor scoring system.[77] This will be used as the main independent measure of sleep quality.

Sleep diaries will be completed for 1 week before the laboratory PSG, and again at the 3-month follow-up assessments. We will use a diary based on the AASM Consensus Sleep Diary,[73] with items added to track sleep medication use and sleepiness and fatigue ratings (0-10 point visual analog scales), and self-reported PAP use. The diary will be used to compute self-reported sleep efficiency (time asleep out of total time in bed), hours of sleep, time to fall asleep, time awake at night, and number of awakenings. This will be used as an independent measure of sleep quality. Participants who cannot complete the paper/pencil diary will be provided with a telephone number they can call to report diary information each morning.

PAP adherence will be monitored remotely using existing data gathering systems. This will be summarized into the proportion of nights (out of 90 nights) with use ≥4 hours. We will also examine mean hours of nightly use for each participant over the 90-day intervention period. We have experience using these procedures in other studies and this process has resulted in data loss rates <10% for PAP use. the proportion of nights (out of 90 nights) with use ≥4 hours will be used as the main independent measure of PAP use.

The Spinal Cord Independence Measure-Self Report (SCIM-SR)[76] will be used to evaluate performance of activities of daily living. The SCIM-SR is a self-report version of the SCIM III, a reliable and valid measure of global disability for patients with SCI/D. The SCIM–SR has 3 subscales: self-care, respiration and sphincter management, and mobility. Scores range from 0-100 and higher scores reflect greater independence. Comparison of the SCIM-SR to the SCIM III showed high correlations between the scales (Pearson's r for the total score=.87; subscales=.81-.87). Since some individuals' in the study will require the assistance of family members or caregivers, for descriptive purposes we will also ask an individual familiar with the patient's level of functioning to complete the SCIM if the patient gives permission for us to do so. The SCIM-SR total and subscales scores (as completed by the patient) will be used as the functional status outcome measure.

The WHOQOL-BREF[74] is a 26-item version of the WHOQOL-100, and is frequently used as an outcome measure in clinical trials. The questionnaire is composed of four domains: physical health, psychological health, social relationships and environment. It also includes one question on overall quality of life and one on general health. Importantly, items on this scale are not dependent on mobility, which is unlikely to change in patients with

SCI/D as a result of improved sleep. The WHOQOL-BREF scores correlate highly (.89 or above) with WHOQOL-100 scores, and demonstrate good discriminant validity, content validity, internal consistency and test-retest reliability. The four WHOQOL-BREF domain scores will be used as main outcome measure.

The Patient Health Questionnaire-9 (PHQ-9)[75] is a 9-item depression module in the PHQ (a self-administered diagnostic instrument for common mental disorders) which is part of the Primary Care Evaluation of Mental Disorders (PRIME-MD) suite of evaluation tools. The PHQ-9 aligns to the DSM-IV diagnostic criteria for depression and is widely used to screen for depression across VA. The PHQ-9 total score will be used to measure depressive symptom severity as an outcome.

The Flinders Fatigue Scale (FFS)[78] is a 7-item fatigue rating scale used to measure general symptoms of fatigue. The FFS has high internal consistency (.91), can discriminate good versus poor sleepers ($p<.0001$) and is sensitive to change over time. The FSS is sensitive to change after sleep-related interventions as well. The FSS total score will be used as an outcome measure.

Spirometry is a simple bedside test used to evaluate lung function. Key spirometry values include forced vital capacity (FVC) and forced expiratory volume over 1 second (FEV1) and the absolute FEV1/FVC ratio. If the FVC and FEV1 are decreased, the absolute FEV1/FVC ratio distinguishes between obstructive and restrictive impairments. A normal absolute FEV1/FVC ratio suggest that restrictive ventilatory impairment may be present, and a reduced FEV1 and absolute FEV1/FVC ratio indicates an obstructive ventilatory pattern. We will use supine FVC and MIP as the key outcome measures for respiratory function for this study, as these are the most representative of respiratory functioning during sleep.

4.5. Data management:

Participants will be assigned unique ID numbers, which will be entered into databases and used on study forms. Using existing protocols, we will secure all records and files in compliance with VA data security policies. Electronic transmissions will be HIPPA compliant, and PAP equipment data transmissions will adhere to data security and data transfer policies. Original study forms will be archived and stored in locked cabinets in approved areas. Datasets will be cleaned by screening for out-of-range values, and comparing a random sample of 10% of entered data to original data collection forms. Problems with data entry will be addressed in an ongoing manner. Double entry procedures will be used on a 10% random sample of cases in each dataset, with additional training and review of data if errors are identified. Cleaned data will be scored and aggregated, then data will be merged into one main database for statistical analyses.

4.6. Data analysis plan:

4.6a. Study Design Considerations: The study design and data analysis will follow the CONSORT criteria for randomized controlled trials (RCTs).[58] Participants will be randomly assigned to the treatment or control group as described in **Section 4.4b**. Randomization should produce groups that differ only by chance at baseline; nevertheless, the adequacy of randomization will be assessed by comparing the groups on all outcomes as measured at baseline. We will follow intention-to-treat (ITT) principles. While we anticipate some participants will not complete the intervention; we will continue to collect follow-up data from all randomized patients whether or not they complete the intervention program to which they are assigned. We anticipate no more than 10% of participants will have missing or incomplete follow-up data. To improve retention and reduce the risk of missing data, participants will be offered monetary incentives for completing follow-up assessments, regardless of whether they complete the intervention. In our recent studies of Veterans with disabilities, we were able to obtain follow-up data for up to 6 months in 92% of randomized participants. We have achieved this high follow-up rate by developing strong relationships with study participants, keeping them engaged and invested in the project, and making necessary accommodations to gather outcome data. While we do not anticipate differential attrition, we will compute the completion rate for each group (BEST and control) and compare completion rates to determine test for differences as a function of group. We will also compare baseline characteristics among those who have complete versus incomplete follow-up data to test for systematic attrition. To preserve the equivalency formed by randomization, ITT analyses will include all randomized participants for hypothesis testing. Since ITT analysis requires complete data, missing data will be imputed using multiple imputation. Sensitivity analyses will be performed comparing the ITT (with imputation) results to results for those with complete data (anticipated N=56). We have allowed for a 10% missing data rate in sample size computations. We anticipate randomizing 62 individuals (31 per group) to achieve a final total sample with complete outcome data at the 3-month follow-up of N=56 (28 per group). We do not anticipate additional attrition after 3 months since follow-up data beyond that time point will be gathered with remote telemonitoring.

Overview of sample size computations: Power computations were performed using the Stata power command. To determine the required sample size for the study, we determined the hypotheses for which we require the largest sample size. In this study, Aim 2 requires the largest sample size (n=56 with complete data; N=62 total randomized). We conducted the power analysis for Aims 1 assuming the sample size of N=56 required to address Aim 2. Given the exploratory nature of Aim 3, these tests were not considered in determining the required sample size for the overall study.

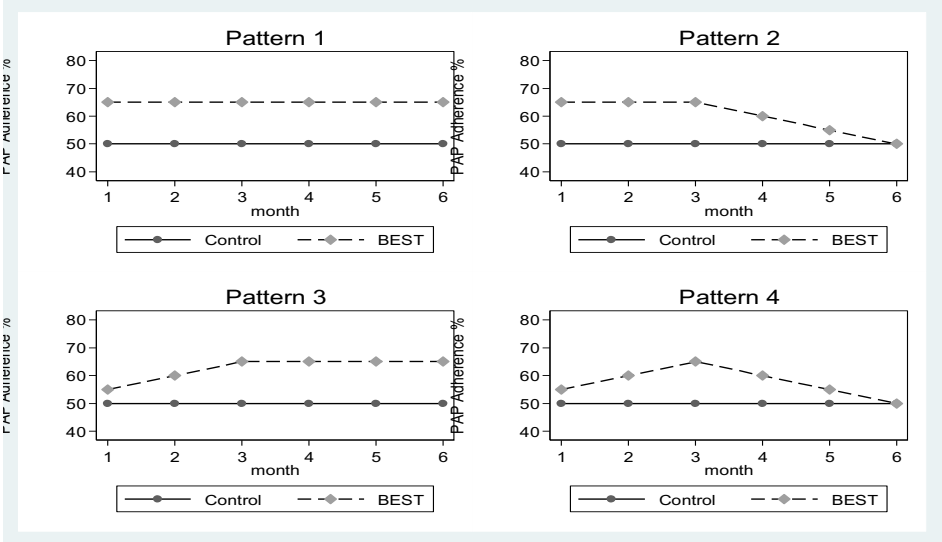
4.6b. Data Analysis and Sample Size Calculation for Aim 1: This aim examines the efficacy of the BEST program on PAP adherence. The main outcome will be the proportion of nights (out of 30 nights) with ≥4 hours of PAP use, as measured by the PAP machine itself. PAP adherence will be computed for the first 30 days (month 1), and for each subsequent 30-day period (months 2-12). All participants will be measured for at least 180 days, thus providing at least 6 months of data for all participants. PAP adherence rates beyond month 6 will be computed for participants who enrolled early enough to provide such data. Because adherence data will be gathered remotely using existing telemonitoring technologies in which PAP machines transmit use data to a cloud-based server, complete data is expected for each person. In an ongoing VA-funded study of PAP adherence being conducted by Dr. Martin's research group, PAP adherence data or confirmed non-use has been obtained in 100% of participants using this method. The proportion of nights a patient uses PAP for 4 or more house will be computed by summing nightly scores (1=PAP used at least 4 hours; 0=PAP used less than 4 hours) and dividing the sum by the number of observations (i.e., 30 nights). Denoting $\hat{p}_{ij}$ as the proportion of nights for person "i" in month "j", the sampling distribution of $\hat{p}_{ij}$ will have an expected value equal to p_i (the true proportion who use PAP in the population in month "i") and the standard deviation of this sampling distribution is equal to sqrt($N*p_i*(1-p_i)$). Further, based on the central limit theorem the sampling distribution of these monthly proportions, $\hat{p}_i$ is expected to be normally distributed, justifying the use of normal theory statistical methods for the analysis of monthly PAP adherence.

Mixed-effects models will be used to compare monthly PAP adherence rates for the BEST program versus control program. When applied to longitudinal designs, mixed-effects models accommodate incomplete data across time points (such as arises in this study where only some participants will have data beyond six months) and can permit specification of a wide variety of residual covariance structures.[78] PAP adherence will be analyzed using a 2 by 12 factorial mixed-effects model with a fixed intercept, where treatment group is a two-level between subjects factor (i.e., BEST versus control) and time is a 12 level categorical repeated measures factor (i.e., month 1, month 2, ... month 12). This approach will allow us to examine potential non-linear trends in the data which would not be readily apparent if time were treated as a continuous variable. The Bayesian Information Criteria (BIC) will be used to identify and select the best fitting residual covariance structure. Using the mixed-effects model, the difference in adherence rates between the BEST program and control group will be assessed and tested at each month.

Hypothesis 1a will be assessed evaluating the significance of the difference in adherence rates between the BEST program and control groups in months 1-3 (during the BEST program intervention).

Hypothesis 1b will be assessed by testing the significance of the difference in adherence rates between the BEST program and control groups in months 4-6 (after the BEST program has ended).

Figure 6 illustrates four possible patterns of results Pattern 1 suggests the BEST program immediately improved PAP adherence and effects were sustained over time. Pattern 2 shows that the BEST program improved PAP adherence during the treatment period; however, effects later diminish. Pattern 3 shows that the BEST program improved PAP adherence gradually during the "treatment" period and effects were sustained over time. Pattern 4 also shows that the BEST program improved PAP adherence gradually; however, effects later diminished. These patterns will be statistically dissected to distinguish between immediate vs. gradual gains in pap adherence during the "treatment" phase, and between "sustained" and "diminishing" effects during the post-treatment phase (refer to Mitchell 2012[79]).



Hypothesis 1c will be assessed by testing the significance of the difference in the adherence rates between the BEST program and control groups in months 6-12. Further analyses will be performed by graphically representing the results (as illustrated in **Figure 6,** with 12 instead of 6 months), and further analyses of treatment maintenance versus diminution of effects will be statistically considered.

Figure 6: Possible patterns of results illuminated by the proposed analysis.

Power Analysis for Hypotheses 1a-c: As described above, the power with respect to Aim 1 was computed assuming a sample size of N=56 with complete data (required to address Aim 2; total N=62). This aim focuses on the difference between the two groups in terms of the average proportion of nights of PAP use ≥4 hours per month. The standard deviation (SD) of this proportion is most conservatively estimated as SD= 0.0913 [computed as sqrt(.5*(1-.5)/30)=.0913]. Given this SD, alpha=0.05 and power=.80, the study can detect a difference in the average proportion of nights of PAP use ≥4 hours of 7% between intervention and control for a given month. In interpreting the results, however, we will focus on larger more clinically-important effects. This study will have ample power to detect these. For example, using the same sample size and alpha, the power to detect a 10% difference between groups would be power=.98. The power to detect a 20% difference would exceed power=.999. We would consider a difference of less than 10% (even if statistically significant) not clinically meaningful. We would consider a difference of 10% or more to be a clinically relevant difference. We would consider a difference of 20% or more to be a moderate and clinically relevant difference, and we would consider a difference of 30% or more to be a substantial and very clinically meaningful difference.

4.6c. Data analysis and Sample Size Calculation for Aim 2: This aim compares outcome measures beyond PAP use that are expected to improve as a result of the BEST program, compared to the control program. The outcome variables tested will include patient-reported sleep quality (hypothesis 2a), overall functioning (hypothesis 2b), quality of life (hypothesis 2c), and respiratory function (hypothesis 2d).

Data Analysis for Hypotheses 2a-d. These hypotheses will be tested using ANCOVA models to compare groups (BEST vs. control) for each of main outcome measured at post-treatment, after adjusting for baseline measurement of the outcome as a covariate. Compared to a "split-plot ANOVA" or an analysis of change scores, this strategy offers greater statistical power and better controls for possible baseline differences.[80]

Power Analysis for Hypotheses 2a-d. Table 7 shows the required sample size as a function of the standardized effect size and the correlation between posttest and baseline scores to achieve 80% power using a two-tailed alpha of 0.05. Cohen[81] describes an effect size of d=0.8 as large, d=0.5 as medium, and d=0.2 as small. **Table 7** focuses on the combination of effect sizes and pretest-posttest correlations that would achieve power of .80. To evaluate plausible pretest-posttest correlations for the measures associated with hypotheses 2a-c, we assessed baseline to 4-month follow-up measures in a RCT of a sleep intervention for Veterans with disabilities. These are presented in detail below for each of the three hypotheses. **Table 7** shows that under the most pessimistic scenario (assuming no correlation between pre-test and post-test measures), this study has sufficient power to detect a large effect (*d*=0.75). As the purpose of this study is to find clinically meaningful effects (i.e., effects that tend to be large), this power analysis suggests sufficient power to detect such effects for all outcome measures. However, our prior research found very substantial pretest/posttest correlations (e.g., r=.75) which would permit detection of smaller effects (i.e., medium effects of d=0.50). Using the lower confidence limits still found substantial correlations (e.g., r=0.56) suggesting that this study will have the ability to detect all effects of d=0.63 or larger with a sample size of n=56 with complete 3-month follow-up data. To achieve this, we will randomize 62 subjects into intervention vs. control.

Table 7. Required total sample size as a function of effect size and pre-test/post-test correlation for 80% power, alpha=.05.

Sample Size	Effect Size (Cohen's d)	Pretest/Posttest Correlation
N=56	d=0.50 (medium)	r=0.75
	d=0.55	r=0.68
	d=0.60	r=0.60
	d=0.63	r=0.56

	d=0.65	r=0.50
	d=0.70	r=0.36
	d=0.75	r=0.00

Hypothesis 2a: To estimate the pretest-posttest correlation, we used our prior research showing a baseline-4-month correlation for PSQI of r=0.74 (95% CI=[.56,.86], N=40). Choosing the lower confidence limit (r=.56) implies sufficient power to detect an effect size of Cohen's d=.63 (an effect somewhat larger than a medium effect) with N=56 (**Table 7**). Choosing the observed correlation (r=.74) implies sufficient power to detect an effect size of Cohen's *d*=.50 (a medium effect). Assuming no correlation (r=0.00), the study could still detect an effect size of Cohen's *d*=.75 (a large effect).

Hypothesis 2b: In the same preliminary data we found the baseline-4-month correlation of instrumental measures of daily living (IADLs) was r=.81 (95% CI=[.67, .89[). Using the lower confidence limit suggests the ability to detect an effect of d=.55 (slightly larger than medium effect).

Hypothesis 2c: To inform the power for this hypothesis, we examined baseline-4-month correlations for PHQ9 and FSS in our prior work. The correlation for PHQ9 was r=.79 (95% CI=[.64,.89], N=40), and for FSS, r=.76 (95% CI=[.57,.87], N=36). Using a conservative approach (lowest lower confidence interval = 0.57), an effect size of 0.63 could be detected with a sample size of 56 (See **Table 7**). Assuming the lowest observed correlation (r=0.76), the study would have sufficient power to detect an effect of d=0.50 (a medium effect). Our **Preliminary Data** shown in section 3.6 indicate large treatment effects comparing a behavioral sleep program vs. attention-control in terms of FSS (ω^2=64%) and PHQ9 (ω^2=35%). We believe similarly "large" effects for these outcomes are likely in the proposed study.

Hypothesis 2d: The main respiratory function outcomes are PFTs (i.e., upright and supine respiratory function/forces) measured at 3-months. While we have no prior data on pretest/posttest correlations for these measures, our prior research has found a the SD for FVC when measured sitting is 17.1, and 15.7 when supine. Considering a 12% change as clinically relevant, this implies an improvement, expressed as Cohen's d=.70 (sitting, 12/17.1) and d=.76 (supine 12/15.7). **Table 7** shows that there would be sufficient power to detect a 12% improvement in sitting respiratory function (corresponding to d=.70) given a correlation of r=.36 in from baseline to 3 months. Likewise, there would be sufficient power to detect a 12% improvement in supine respiratory function (corresponding to d=.76) regardless of the size of the correlation.

4.6d: Analysis plan for Exploratory Aim 3: This aim considers whether the BEST program is more effective for subgroups of patients such as those with depression, insomnia or bladder dysfunction. For categorical measures, grouping variables will be coded as 0/1. For continuous measures (such as ISI score), participants will be categorized into groups, using clinical cutoffs. If such cutoffs yield highly imbalanced groupings, we will consider a median split. For a given variable, each grouping variable will be interacted with treatment group and introduced into each analysis described in Aims 1 and 2. The test of the interaction will assess whether the treatment is more effective for one subgroup than another.

5. Dissemination Plan

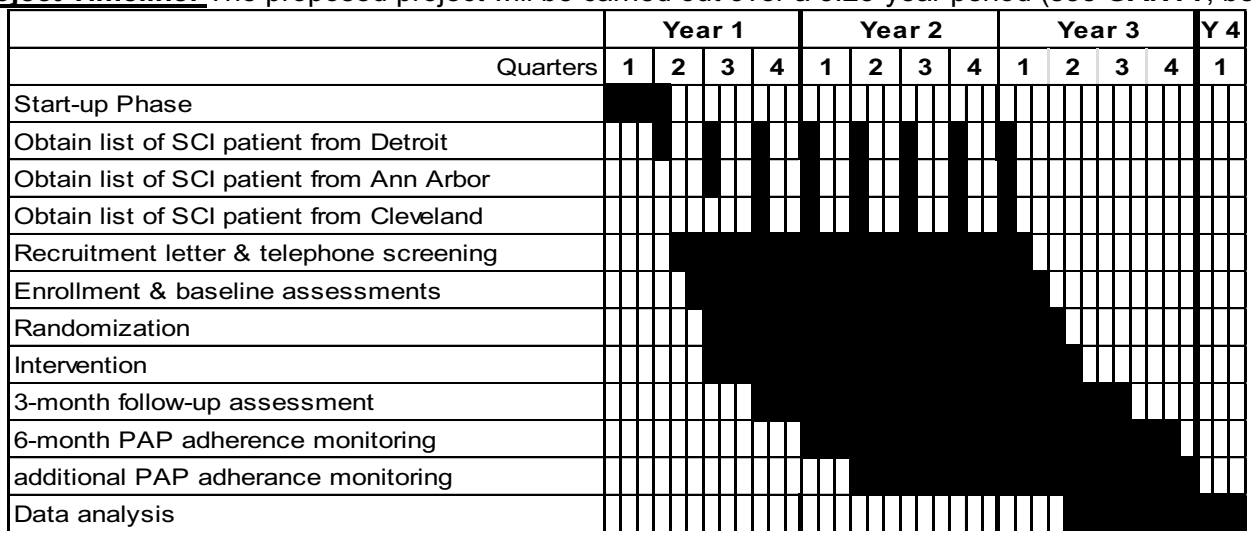
5.1. Dissemination to the Scientific Community: We intend to present the results of this study at national conferences on sleep and SCI/D, and to publish the results in peer-reviewed scientific journals. When possible, we will also take advantage of opportunities for dissemination of these findings available through VA Centers focused on SCI/D (e.g., VA HSR&D QUERI Center), such as in newsletters and lecture series.

5.2. Dissemination to VA providers: We anticipate that results will show the BEST program is effective in improving PAP adherence and that treatment of SDB will improve multiple patient outcomes. In that case, there will be immediate impact of the results on clinical care at our facility, as the BEST program can immediately become part of routine care for our SCI/D patients. We will also seek additional funding for a multi-site trial. We anticipate that such a trial would first focus on facilities with sleep medicine providers and SCI/D clinics. At the conclusion of this line of research, we will have a well-developed, useful clinical approach to managing SDB among SCI/D patients. We have employed the RE-AIM[82] framework in designing and developing this treatment study making the likelihood of "clinical update" more feasible. Using this framework, we have designed a program that can ultimately be used in clinical settings.

We will also disseminate findings through the VA Sleep Network. In discussing this project at a national meeting of VA Sleep Providers in 2014, there was a great deal of interest from Centers in participating in a future multisite trial, as many recognize the challenges associated with treatment of SDB these patients.

6. Project Management:

6.1. Project Timeline: The proposed project will be carried out over a 3.25-year period (see **GANTT**, below).



6.2. Coordination across sites:

Human subjects activities will be carried out at JDDVAMC in Detroit, MI where Drs. Badr and Sankri are based. They will oversee day-to-day operations and supervise staff. Drs. Martin, Fung and Mitchell are based at VAGLAHS. Drs. Martin, Fung and Mitchell will participate in Dr. Badr's monthly research team meetings by phone or video conference, and Drs. Martin, and Fung will travel to Detroit for investigators' meetings. Dr. Martin will play an ongoing role in weekly oversight of the patient education component of the BEST program. She has served in this consultative role through VA's Evidence Based Psychotherapy dissemination programs, and for other VA-funded research projects. Since the study statistician is based at VAGLAHS, we will use established procedures for secure data transfer between sites (e.g., shared network drive), and we will follow all current VA Policies regarding data transfer and security. We have experience transferring data between the two sites in accordance with VA regulations for previously conducted analyses.

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