A. SPECIFIC AIMS

Obesity and sedentary lifestyle are associated with poor glucose control in persons with type 2 diabetes mellitus (T2DM) and resistance to behavioral interventions. While **diabetes self-management education and counseling** (**DEC**) has been improved and refined over the last 30 years, many persons with T2DM continue to have difficulty in achieving glycemic goals.[1,2] Excessive daytime sleepiness, a frequent problem associated with obstructive sleep apnea (OSA), is a likely barrier to self-management of T2DM. The prevalence of OSA in persons withT2DM is notably greater than that for the general population, estimated to range from 40% to 97% depending on the degree of OSA severity and the age of the sample.[3-6] In addition, results of previous studies suggest that OSA and T2DM not only co-exist but that sleep-related breathing disorders directly adversely affect glucose homeostasis. [7-14] The most effective medical treatment for OSA is CPAP which eliminates apneas and hypopneas during sleep, and results in improved self-reported daytime functioning.[15-18] Unfortunately, there is a notable gap in our understanding of the association between OSA and T2DM. The effect of CPAP treatment on glucose control remains unclear, with conflicting results possibly related to the previous studies having small sample sizes[15-20] and not intervening in behavioral aspects of glycemic control. Therefore, the effect of OSA on behavioral aspects of diabetes self-management and the effect of CPAP treatment on diabetes education and counseling (DEC) remains unknown.

Data from our preliminary studies in persons with T2DM suggest that excessive daytime sleepiness may be a barrier to effective diabetes self-management and that poor sleep is associated with suboptimal diabetes self-management.[21,22] We recently completed the *OSA, Sleepiness and Activity in Diabetes Management* study (OSA-DM) a double blind, randomized, placebo-controlled pilot study (R21 HL 089522, PI, E. Chasens), that compared physical activity and glycemic control in adults with T2DM treated with active CPAP vs. those on sham-CPAP. Our preliminary data analysis suggests that CPAP treatment of OSA improves glycemic control and increases physical activity in persons with T2DM. Hence, we demonstrated the feasibility to recruit and retain subjects, a requirement for undertaking a larger study to test the efficacy of CPAP treatment in moderate-to-severe OSA in adults with T2DM.

The underlying premise of the proposed study from this new investigator is that OSA hinders diabetes self-management in adults with T2DM. The next step in understanding the effect of OSA on diabetes self-management is to determine the efficacy of CPAP treatment in improving diabetes outcomes in adults treated with CPAP compared to those on sham-CPAP. This proposal differs from the pilot/feasibility study in that we have a broader set of health outcomes that we are testing. We propose to enroll 210 adults with T2DM and moderate-to-severe OSA who have suboptimal diabetes self-management. We will conduct a 12-week double blind, randomized, placebo-controlled trial to determine if diabetes self-management outcomes and glycemic control are superior in subjects with OSA who are treated with CPAP and receive a DEC (**CPAP + DEC**) compared to control subjects (**sham-CPAP + DEC**). We will also explore the effect and robustness of treatment with CPAP (after 24-weeks) on glycemic control and factors associated with diabetes self-management.

Aim 1 (Primary): To determine if CPAP + DEC is superior to sham-CPAP + DEC for improving glycemic control. **H1:** Subjects who receive CPAP + DEC will have improved glycemic control compared to subjects with sham-CPAP + DEC at 6 weeks and 12 weeks.

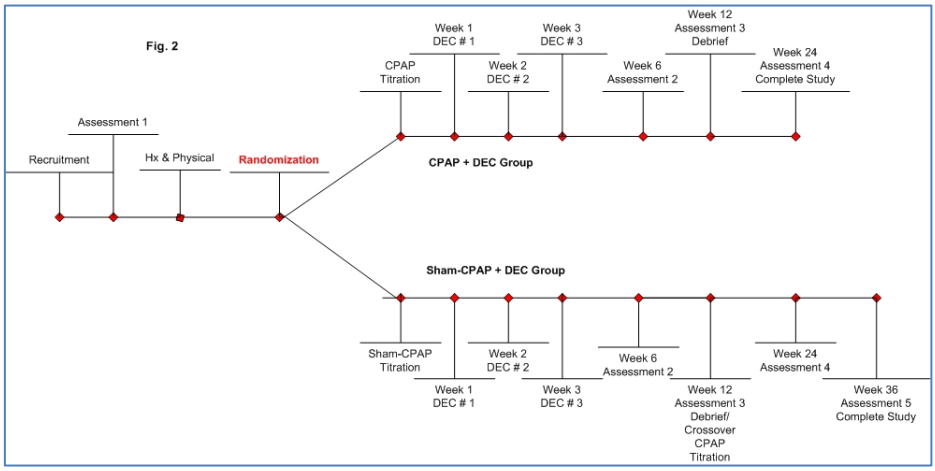
Aim 2 (Secondary): To determine if CPAP + DEC is superior to sham-CPAP + DEC for improving diabetes self-management outcomes. **H2:** Subjects who receive CPAP + DEC will have better diabetes self-management outcomes (retention of information taught during the DEC classes**,** improved self-management behaviors**,** diabetes monitoring activities**,** increased physical activity, and decreased diabetes-related distress compared to subjects with sham-CPAP + DEC at 6 weeks and 12 weeks.

Aim 3: To explore adherence to CPAP (dose) and specific neuro-behavioral and physiological mechanisms (sleep quality, daytime sleepiness, mood, and vigilance that may mediate the effects of CPAP treatment on glycemic control and diabetes self-management outcomes (6 weeks and 12 weeks).

Aim 4: To explore the association between the durability of treatment of OSA (i.e. adherence to CPAP) and sleep quality**,** daytime sleepiness, mood, diabetes self-management, and glycemic control after 24 weeks of active CPAP in the full sample.

B. PROTOCOL

Design. We will use a 2-group, randomized controlled design with treatment cross-over. Adults with T2DM who have an AHI ≥ 10 and suboptimal diabetes management, defined as an A1C ≥ 6.5.0%, will be randomized to one of two conditions: CPAP + DEC vs. control group - sham-CPAP + DEC (see Figure 2). We will compare the primary outcomes between the two groups on 1) glycemic control and 2) diabetes self-management outcomes. After cross-over, we will pool subject's 6 months data to evaluate robustness of treatment effects.



Subjects and Recruitment

We will recruit adults with T2DM who are at high risk for OSA and suboptimal diabetes management from UPMC diabetes and sleep clinics in the Pittsburgh area (Monroeville, Mount Lebanon, and Mt. Nebo) in addition to the Oakland site, the community, and the Veterans Administration Pittsburgh Healthcare System (VAPHS).

At West Virginia University the following methods will be utilized to identify potential subjects: EPIC electronic medical record review, work with primary care providers in the Family Medicine, Medical Group Practice, and Medical Specialties clinics. Brochures describing the trial will be made available in the outpatient settings.

University of Pittsburgh will enhance strategies that were successful in the pilot/feasibility study by using resources from the Clinical & Translational Science Institute (CTSI), which has developed community partnerships to assist in the recruitment of minorities. We will also recruit from completed studies and research registries by having letters sent to former participants in those studies. The PI/Project Manager and their staff of studies or research registries will identify the participants who may be appropriate to receive the letter and will send the letters. We will utilize social media advertisements developed by TrialSpark to recruit for the study. Potential participants are screened on-line after they have indicated their consent, they will receive follow-up email messages informing them if they are eligible. Those persons who are potentially eligible will receive telephone phone calls to confirm their eligibility and to set up an appointment for the first assessment. If individuals who receive the letter are interested in potentially participation in the DSTT study, they will be provided on the letter with DSTT contact information to obtain further study information. We will embed research staff in VAPHS and UPMC clinics to recruit subjects. We have initial contacts with the Hispanic Chamber of Commerce and the Latino Roundtable of Pittsburgh. We will directly recruit subjects by attending community events, speaking at public health events, placing flyers in the community, and through newspaper advertisements. We will expand recruitment by the co-investigators (Drs. Atwood, Korytkowski, and Strollo) speaking to medical providers in internal medicine, geriatric medicine, public health, women's health, sleep, and diabetes clinics to discuss the study and encourage referral of potential subjects at the University of Pittsburgh and at the VAPHS. Drs. Rao and Atwood at the VAPHS will assist in identifying potential patients. We will develop pocket guides on the purpose of the study and inclusion/ exclusion criteria for medical providers.

A brochure and flyer describing the study will be created for distribution; a "Dear Patient" letter will be generated for distribution to patients scheduled for diabetes and/or sleep clinic visits; a "Dear Colleague" letter will be generated and distributed to primary care, and women's health physicians in the community; newspaper advertisements describing the study and seeking individuals who snore will be circulated in the local newspapers. Dr. Susan Redline will act as a consultant on recruitment.

Eligibility criteria:

When the potential subjects have met the initial eligibility criteria, and before the sleep study is conducted, their PCP will be contacted by the study coordinator to inform him/her of the potential subject's study participation and ask for their approval, if appropriate.

The following criteria must be met for subjects to be randomized into the study:

1) T2DM with suboptimal glucose control (A1C ≥ 6.5%),[87,88]

2) AHI greater than ≥ 10 (ApneaLinkPlus®,

3) Age 18 years or older
4) Willing to be randomized to CPAP or sham-CPAP.

Exclusion criteria include:

1.) A1C > 11
2.) Gestational or type 1 DM
3.) Sleep duration < 4 hrs per day
4.) Change in diabetes medications during the previous 3 months
5.) Acute medical or surgical conditions or hospitalization ≤ 3 months (e.g. angina, stroke, major surgery, major depression or serious psychiatric conditions)
6.) Previous diagnosis of another sleep disorder, oxygen or bi-level PAP required
7.) O_2 sat. < 75% for > 25% of the ApneaLinkPlus sleep study
8.) Cardiovascular events noted during overnight titration sleep study,
9.) Prior CPAP
10.) Persons in household with CPAP
11.) History of near-miss or auto accident during last 12 months
12.) Employed in safety sensitive job (i.e. truck driver or airline pilot)
13.) Non-ambulatory
14.) Regular use of hypnotic or alerting (e.g. modafinil) medications
15.) Excessive consumption of alcohol.

Men: > 4 drinks a day and more than 14 drinks per week

Women: > 3 drinks a day and > 7 drinks per week

16.) Claustrophobia to wearing mask
17.) Unable to speak, read & write English
18.) Pregnancy
19. Request of PCP

Exclusion criteria were determined to maintain subject safety and study integrity.

Intervention and sham.

Subjects in both arms of the study will be treated with the Respironics System One Auto CPAP System. This system contains a wireless modem (Respironics EncoreAnywhere™) that records adherence to CPAP nightly treatment and transmits the data to a password protected, web-based secure server. During the entire protocol, CPAP machines will be provided free of charge to the subjects; CPAP machines are being provided by the manufacturer (see Respironics, Inc. Letter of Support). A standardized procedure to ensure adherence will be utilized in both treatment arms. The EncoreAnywhere™ system will record data for the entire time CPAP is in use. The Sleep Educator will upload participant adherence data from the EncoreAnywhere™ system on a regular (weekly) basis.

A sham circuit, a modification of the design of Farré and co-workers[89] manufactured by Respironics Inc., will create a CPAP placebo. This device was utilized by T. Weaver (CATNAP study) and by C. Kushida (APPLES study). This design places a hidden leak and a restrictor in the connector (Respironics, Inc WhisperSwivel®) between the mask and CPAP tubing that allows air to escape and to prevent the rebreathing of carbon dioxide. The pressure will be set to 0.5-1 cm H_2O at the mask to generate sufficient airflow to convince the CPAP naïve subject that they are receiving treatment, however; the pressure is insufficient to hold open the pharynx. The airflow generates a similar degree of blower noise from both circuits, providing CPAP naïve subjects with audible and tactile cues that do not differ between sham and active-CPAP and thus maintains blinding. The only difference between the two circuits is the mask pressure, which is the desired variable to be blinded. Data demonstrate that the sham-CPAP does not deliver therapeutic pressure nor produce clinically meaningful alterations in pre-treatment AHI, the nadir of oxygen desaturation, arousal index, and sleep efficiency.[90,91] This design was used successfully by our research team in the pilot/feasibility study with subjects remaining blinded (p = .67) to the group assignment.

Length of the intervention. The duration of the blinded intervention with sham comparison is 12 wks. This is based on previous studies in OSA patients demonstrating that improvements of objective sleepiness plateaus after 2 wks of treatment,[94] results that are supported by several clinical trials that found significant improvement after 4 wks of CPAP treatment in subjective sleepiness,[44-47] objective sleepiness,[45,47] neuro-behavior outcomes,[44] mood,[45] and functional status.[45,47] After the completion of the intervention, we will provide CPAP treatment to those subjects who were initially

randomized to sham-CPAP. We will follow all subjects for a total of 24 weeks of therapeutic CPAP treatment to evaluation durability of adherence to CPAP, glycemic control, and behavioral outcomes.

CPAP Titration Study/Sham-CPAP Titration. The nighttime CPAP titration PSG will be performed to determine the optimal level of CPAP needed to eliminate the subject's apnea. The CPAP titration PSG will be performed using standard techniques,[92] with effective CPAP level defined as an AHI <5/hr with the minimum effective pressure for each subject. Patients randomized to the sham-CPAP arm will have titration studies that are performed identically to the CPAP titration except the standard CPAP connection will have a sham-CPAP restrictor piece added, the modified expiratory valve will be attached and pressure at the nose mask will be ≤ 1 cm H2O. The WhisperSwivel® connectors (sham and regular connectors) will be coded for the active CPAP intervention or the sham-CPAP group. A trained research Registered Polysomnographic Technologist at will choose the appropriate connector and record the number and the group (CPAP/sham-CPAP) in a secure file; this person is unblinded. The sham CPAP blower will be set at a pre-set level (this pressure is not transmitted to the subject, but determines the blower sound). The level of pressure for the blower of each sham CPAP participant will be displayed to participants as a "10 cm of H^2O".

Setting.
The N-CTRC, located at Western Psychiatric Institute and Clinic (WPIC), will be the site for all sleep studies (see letter of support Dr. Daniel Buysse) for University of Pittsburgh recruited. The setting for all assessments will be the VAPHS for subjects recruited there. . Montefiore Hospital CTRC (MUH-CTRC) will be the site for all University of Pittsburgh recruited participants.

West Virginia University: Subjects will be consented and undergo study procedures at the WVU Medicine outpatient clinics (Sleep Evaluation Center, Medical Group Practice, Family Medicine, and Medical Specialties clinics), and the Clinical Trials Research Unit.

Study Measures. (See Appendix for copies of instruments). We selected the self-report and physiological measures to reflect the key behavioral domains that are adversely affected by OSA and EDS as documented by numerous published studies. They provide a comprehensive assessment of treatment response and the basis for secondary analyses and hypothesis generation. The tests are organized to reduce subject burden. Data from the pilot study indicate that the clinical assessments can be completed in < 1 hour, and questionnaires can be completed in the subject's home at their leisure. We recognize the need to decrease subject burden and have reduced the number of visits by having the subjects' return their devices (ApneaLinkPlus®, Body Media SenseWear Pro Armband®) by mail, a strategy that was successful in the pilot/feasibility study.

Screening Measures:
Screening interview. Respondents to recruitment solicitations will undergo a brief interview (in-person or telephone) to determine if they meet initial eligibility criteria. The interview includes the MAP Index.
Multivariable Apnea Prediction (MAP) Index [93] will be used to identify persons at moderate-to-high risk for OSA. The MAP uses the frequency of snoring, breath holding, and snorting, age, sex, and self- reported height and weight to determine the likelihood of OSA. The MAP estimates using multiple logistic regression; its positive predictive ability of AHI≥10 in patients presenting at sleep disorders centers was 0.79 ($p<0.0001$).
ApneaLinkPlus® is an FDA approved level III device for in-home unattended sleep studies (see Figure 3). Previous studies found the device to be highly sensitive and specific to diagnose moderate-to-severe OSA. [94-96] The clinical guideline by the Portable Monitoring Task Force of the American Academy of Sleep Medicine concluded that level III portable devices were appropriate for the diagnosis of OSA in patients with a high pretest probability of moderate-to-severe sleep apnea.[97] The older single channel ApneaLink was evaluated in determining the presence and severity of OSA in a recent study by Drs. Atwood and Strollo.[98] In a sample (mean age 45.1 ± 11.3, 55% female, BMI 35.9 ± 9.1) that will be similar to ours, the ApneaLink had a sensitivity of 79.0% and specificity of 88.2% for detecting an AHI ≥ 15; for an AHI≥ 20 the sensitivity was 100.0% and specificity 92.5% compared to a simultaneous in-laboratory polysomnography. The ApneaLinkPlus® that we will use is a 4-channel device that records breaths, respiratory flow, oxygen saturation and pulse rate. We will ask enrolled participants to wear the ApneaLinkPlus® for a single night to identify those persons with ≥10 apneas/hour. The ApneaLinkPlus® has scoring software version v9.2 that analyzes data. Drs. Atwood, Strollo (University of Pittsburgh/VAPHS), or Stansbury (West Virginia University) will review all ApneaLinkPlus® studies. At the John Dingel VAHS, a similar FDA approved level III device, the NOX-T3, will be used. This device provides the same metrics as the ApneaLink Plus®.

Primary Dependent Measures

Aim 1: Glycemic control. Objective measures of glycemic control are 1) A1C and 2) serum fructosamine

a. The A1C (5 cc serum sample) offers a stable indication of glycemic control over the past 2 to 3 months. The American College of Endocrinology suggests a goal of an A1C of 6.5% or less. [99] We will utilize the use of only standardized, in-laboratory validated assays for A1C testing.

b. The fructosamine level (5cc serum sample) measures glycation of serum proteins, it is responsive to changes in the patient's average glucose because the half-life of albumin (about 20 days) is of shorter duration then the A1C. This test will show any change in glycemic control over the last 2 to 3 wks. (*Optional measure, not done at WVU*)

Aim 2: Diabetes self-management behavior

a. The Diabetes Knowledge Test (DKT)[100] We will use the first 15 items for subjects who do not use insulin and the additional 3 on insulin usage for subjects who are prescribed insulin. The psychometric properties of the items yield an alpha ≥ 0.70 for the general test and the insulin-use subscale, which indicates that both are reliable. The DKT takes approximately 5-10 minutes to complete.

b. The Summary of Diabetes Self-Care Activities (SDSCA)[101] is a brief questionnaire about diabetes self-management that includes items assessing the following aspects of the diabetes regimen: general diet, specific diet, exercise, blood-glucose testing, foot care, and smoking. This validated instrument has high inter-item correlations within scales (mean r = 0.47), with the exception of specific diet; test-retest correlations were moderate (mean = 0.40). It takes 5-10 minutes to complete.

c. Removed the Diabetes Care Profile (DCP) from protocol.

d. The Body Media SenseWear Pro Armband® provides an objective measurement of physical activity. It was used successfully in the pilot/feasibility study and will be used to obtain 7-day 24-hour activity counts. The Body Media SenseWear Pro Armband® measures the duration and intensity of activity (daily total energy expenditure, number of steps walked, average metabolic equivalent, active energy expenditure) individuals.[102] It was found accurate in measuring sedentary to high-impact activity; it collects data on sleep duration which can be evaluated along with the sleep diary. The armband allows activity not captured directly, such as water aerobics, to be manually entered; the software then utilizes an algorithm to determine the energy expenditure. The data will be uploaded to a computer, minimizing the potential for recording errors. The activity endpoint will be summarized as the subject's mean daily activity count on days when the monitor is worn ≥ 20 hours. (At site WVU, the BodyMedia SenseWear Pro Armband® is not used. A pedometer will be used to obtain the steps walked).

e. The Problem Areas in Diabetes (PAID)[103] will be used to assess emotional distress related to diabetes management and how it is affected by OSA and EDS. The PAID comprises 24 items on a 5-point Likert scale that are summed to provide a total score of emotional distress, with higher scores denoting greater distress. The internal reliability is >0.90; it has sound concurrent validity as determined by moderate to strong correlations with a range of theoretically-related measures, and responsiveness to change during brief psychosocial and educational interventions.[103,104] Welch et al.[105] showed effect sizes between .30 and .65 for the PAID across seven different intensive diabetes psychosocial, educational, and medical interventions, indicating good responsiveness. The PAID has demonstrated validity among minority urban patient populations.[106] It takes 5-10 minutes to complete.

Secondary Dependent Measures:

a. Sleep Quality. The Pittsburgh Sleep Quality Index (PSQI)[75] is a validated questionnaire that measures the quality, duration, and patterns of sleep in adults. It differentiates "poor" from "good" sleep over the past month. A global sum of 5 or more indicates a poor sleeper. The PSQI has a Cronbach's alpha of .83 and a test-retest correlation coefficient of 0.85. The PSQI takes 5 minutes to complete.

b. Subjective Sleepiness. The Epworth Sleepiness Scale (ESS)[74,110] is an 8-item scale that measures subjective daytime sleepiness, respondents are asked to rate the likelihood of falling asleep in situations using a 4-point Likert scale ranging from 0 ("never dozing") to 3 ("high chance of dozing"). The ESS has test–retest reliability (r=.82) and internal consistency (Cronbach's alpha =.88) . The ESS at ≥ 10 has a sensitivity of 93.5% and a specificity of 100% for distinguishing pathological sleepiness.[111] The ESS takes 2-3 minutes to complete.

c. Mood. The Profile of Mood States (POMS)[76] is a reliable and valid measure of mood states that has been shown to be sensitive to sleep deprivation[53] and to CPAP treatment of apnea.[48] It presents 65 adjectives to rate (1 to 5) feelings during the last 7 days. The POMS takes 5 – 10 minutes to complete.

d. Vigilance. The Brief Psychomotor Vigilance Test (PVT-B).[113] will assess vigilance before and after each DEC session. The PVT-B is a computer-based reaction time test that was recently developed to evaluate the ability to sustain attention and respond in a timely manner to a signal during a 3-minute testing session. There is no difference in sensitivity to sleep loss between the PVT and the PVT-B with the lapse threshold reduced from 500 to 355ms. Total lapses, false starts, and reaction time will be the outcome measures of the PVT-B.

e. Diabetes Empowerment Scale-Short Form measures the psychosocial self-efficacy of people with diabetes. In order to allow for a brief overall assessment of diabetes related psychosocial self-efficacy, an eight-item short form of the DES (the DES-SF) was developed. The DES-SF was created by choosing items from the original 37 items. The reliability of the DES-SF using the original data set was alpha = 0.85.

Additional measures: Demographic, Anthropometric Measures, and Process Measures,

a) Sociodemographic and Lifestyle Questionnaire.[116] Sociodemographic information will be obtained by a questionnaire developed for the Center for Research in Chronic Disorders at the University of Pittsburgh.

b) Health History Questionnaire is a revision of the Charleson Comorbidity Index [117] to capture key information related to comorbid conditions and specific questions of interest such as duration of T2DM and medications

c) BMI/ Body Composition. Height will be measured at baseline. The Tanita-300GS Scale and Body Fat Analyzer will be used to weigh subjects and determine body composition. (Regular scale used to weight subjects at WVU)

d) AADE7 Goal Sheet will be used by the CDE to evaluate progress of self-care activity.

e) Newest Vital Sign (NVS)[118] serves as a screening test for limited health literacy. The NVS is administered using an enlarged, laminated food label that requires interpretation of the information and basic calculations of percent calories and fat (we will offer paper/pencil for calculation); less than 4 correct answers indicate the possibility of limited health literacy.

f) Adherence. EncoreAnywhere™ will be used in the CPAP machines to measure adherence. EncoreAnywhere will be used to measure adherence. The online adherence data will be at least twice during the first week and then weekly. Because increased doses of CPAP are associated with improved daytime functioning, [80] we plan to encourage subjects to be adherent to CPAP/sham-CPAP all-night, every night. We will objectively measure the pattern of CPAP adherence to determine if the subject is a "good user" or "slowly improves" or has less than optimal use and requires focused CPAP support to assist with improved CPAP usage.[109] If we are unable to use the Encore Anywhere device, we will verbally ask participants how many hours they have used the device and check for adherence with data automatically collected in the devices memory that can be downloaded and read from the SmartCard.

g) Activity monitoring will be measured with Omron pedometers. Mean steps walked with the pedometers will be compared to individualized goal for steps based on baseline status during the DEC sessions.

h) Sleep/Activity Diary will be used to record subjective sleep quality and duration, daytime sleepiness, and sleep habits.

i) Food Diary will be used to record dietary intake for 3 days before the DEC. Diet data will be used by the Diabetes Educator to provide participants feedback and help improve eating behaviors.

j) Connor Diet Habit Survey (Connor DHS)[119] will assess eating habits and diet composition. The Connor DHS is a 38-item multiple-choice questionnaire comprised of 5 sub-scales: (a) cholesterol-saturated fat, (b) carbohydrate, (c) beverage, (d) salt, and (e) restaurant eating and recipes. Validity of the DHS was established previously with 24-hour dietary recalls ($r = .33$, $p < .01$). The Connor DHS requires about 5-10 minutes to complete. The Connor DHS will be used at baseline and 6 months.

k) Rapid Eating and Activity Assessment for Patients (REAP). [107]is a dietary assessment tool to briefly assess patient's diet and physical activity. The REAP is a validated instrument with test-retest reliability ($r=.86$, $p<.001$) and convergent reliability with the Healthy Eating Index[108] score ($r=.49$, $p<.0007$). This instrument takes about 10 minutes to complete.

l) SF-12v2 Health Survey is a short (12 questions) version of the SF-36v2® Health Survey that measures a patient's subjective functional health and well-being. The SF-12v2 is a reliable and valid instrument that contains the same structure as the SF-36v2 with Component Summary Measures (Physical Health and Mental Health) and Scales (Physical Health: Physical Functioning, Role-Physical, Bodily Pain, General Health; Mental Health: Vitality, Social Functioning, Role-Emotional, and Mental Health). The SF-12v2 takes approximately two to three minutes to complete.

m) Stanford Sleepiness Scale.[112] Sleepiness varies during the day. The Stanford Sleepiness Scales, a single question that queries sleepiness on a 1-10 scale, is a validated measure of sleepiness or alertness at a specific moment in time. It will be asked before and immediately after each diabetes educational/counseling session.

Procedures

Assessment 1. Written and verbal explanation of the purpose, protocol, risks and benefits of the study will be provided and informed written consent will be obtained. The subject's ability to read at the 5th grade reading level and comprehend information will be evaluated with questions that ask "if you feel sleepy, should you drive a car or use dangerous machines?" Health literacy will be evaluated by the Newest Vital Sign.[118] A urine pregnancy test will be done, if appropriate. Study staff will perform anthropometric measurements (height, weight, body composition) and a

venipuncture to obtain no more than 30 cc blood for A1C, fructosamine, and lipid profile. Waist circumference will be measured twice with an inelastic measuring tape. The Project Manager/ Study Coordinator will instruct subjects on how to wear the ApneaLinkPlus® device that night when they go to sleep. Subjects' will be instructed on wearing the SenseWear Armband® and filling out the Sleep/Activity/Diet Diary when they wake up and before bedtime for the next 7 days. Subjects will be instructed how to complete the questionnaires at home during the next week. They will be given two padded pre-paid mail packets: the first for returning the ApneaLinkPlus® the next day and the second to return the SenseWear Armband, questionnaires, and the Sleep/Activity /Diet Diary after using them for 7 days. Data from the ApneaLinkPlus® will be uploaded and data reviewed by either Drs. Atwood or Strollo (at Pitt/VAPHS) or Stansbury (at WVU) to determine the AHI. When the ApneaLinkPlus® is uploaded, if there is inadequate data to determine AHI eligibility, we will contact the participant and ask if they would be willing to repeat the ApneaLinkPlus® at home sleep study.

History and Physical. Subjects will have a history & physical by a Nurse Practitioner or Medical Fellow to determine if there is any factor that may exclude them from the study. Drs. Atwood, Strollo or Stansbury will determine if subjects meet all study criteria for randomization.

Randomization. Subjects who meet all inclusion/exclusion criteria will be randomly assigned by computer program (R-track®) using a minimization algorithm with equal allocation to one of two treatment groups: 1) active CPAP set at a level of pressure that will abolish nocturnal respiratory disturbances, or 2) sham-CPAP (placebo) where the level of pressure will not abolish nocturnal respiratory disturbances. Use of a minimization algorithm will insure treatment balance on three factors: 1) the participant's baseline physical activity levels in terms of mean number of steps per day based on the SenseWear Armband® ($< 5{,}000$, ≥ 5000),[120] 2) whether the subject had previous diabetes education, and 3) whether the subject is prescribed insulin. Minimization is a form of adaptive treatment allocation in which the probability of assignment to the treatment groups does not remain constant, but is determined by the current balance and/or composition of the groups. Treatment group assignment will be generated and stored in a secured database. Subjects and all research team personnel involved in further data collection will be blinded as to which group the subjects are assigned. The University of Pittsburgh site will randomize participants from all the recruitment sites (West Virginia University, VAPSHS, University of Pittsburgh).

CPAP Titration Study/Sham-CPAP Titration. The nighttime CPAP titration PSG will be performed in to determine the optimal level of CPAP needed to eliminate the subject's apnea. The CPAP titration PSG will be performed using standard techniques,[92] with effective CPAP level defined as an AHI <5/hr with the minimum effective pressure for each subject. Subjects randomized to the sham-CPAP arm will have titration studies that are performed identically to the CPAP titration except the standard CPAP hose will be replaced with the sham-CPAP hose, the modified expiratory valve will be attached and pressure at the nose mask will be $\leq$ 1 cm H2O. The sham CPAP blower will be set at a pre-set level where pressure is not transmitted to the subject but produces the blower sound. Subjects will be loaned, without charge, either the CPAP or the sham-CPAP machines to take home for 12-wks. Subjects and their bed partners' will be instructed by the Sleep Educator on how to improve their sleep hygiene, OSA and CPAP therapy. Subjects will be encouraged to use CPAP/sham-CPAP every night; adherence will be monitored weekly with the EncoreAnywhere™ system.

Diabetes Education/Counseling. The DEC will consist of two (2) one-on-one sessions (a 90 minute session and a 60 minute session), and a minimum of 3 follow-up phone calls of approximately 15-30 minutes with a diabetes educator that will start approximately one week after subjects have started CPAP or sham-CPAP. (see Appendix for Curriculum). Subject education will be provided using published educational materials from the American Diabetes Association and the American Association of Diabetes Educators. Partners will be encouraged to attend the sessions. Data from a RCT suggests that 3 1-hr individual sessions results in significantly (p-values <.05) decreased A1C and stress associated with diabetes management compared to 8-hrs of group sessions.[121] Although the content will be interactive and tailored to match each individual's needs and cultural influences, all subjects will receive standardized DEC based on the AADE patient competencies (AADE7).[39] Subjects will be provided a pedometer to wear each day and a daily goal of steps, which will be increased over the 12 weeks to reach at least 7,500 steps per day.[122] They will be given 7-day paper diaries and asked to record their daily food and beverage intake, physical activity and sleep habits. The diabetes educator will review the diaries at each of the two intervention sessions; will provide written and oral feedback on progress made toward improving their eating and physical activity habits. Subjects will be instructed on the value of self-monitoring diet and exercise to monitor progress to their behavior change goals.[123] Subjects will be questioned on sleepiness before and after the session with the Stanford Sleepiness Scale.[112] Vigilance will be tested before and after each DEC session with the

PVT-B.[113] (Clarification in protocol 7.25.2018): The Stanford Sleepiness Scale is a part of the PVT-B Vigilance test. The West Virginia University site does not perform the PVT-B testing.

Promotion and Assessment of CPAP Adherence. Our goal is for subjects to use their CPAP/sham CPAP all night/every night. We will enhance the procedures for the promotion of adherence that we employed successfully during the pilot/feasibility study. The education was refined from the protocol developed by Dr. T. Weaver; she will be assisting this proposal as a Consultant. We will utilize motivational enhancing problem solving and review and reinforce principles of good sleep hygiene.[124] Subjects will receive education prior to starting CPAP therapy, e.g., that comfort is improved with the use of heated humidification on CPAP machines.[125] All subjects will be shown various masks and permitted to select the most comfortable mask interface. Brochures will be developed in simple language describing the study and stressing the importance of using the treatment every night. CPAP adherence will be encouraged with a phone call to the subjects by a Sleep Educator after the first night of home use. A refinement from the previous study will be that a Sleep Educator will evaluate CPAP/sham-CPAP adherence nightly for the first 2 nights then at least twice weekly with the EncoreAnywhere™ web-based patient compliance system. The Sleep Educator will phone the subjects at least weekly, and intervene to increase adherence.

Assessment 2. An assessment will be done after 6-wks of CPAP/sham-CPAP use. Subjects will be mailed the questionnaires, SenseWear Armband® and the Sleep/Activity/Diet Diary to use for 7-days. They will return to the study site with these items and their glucose meter and pedometer. The assessment includes anthropometric measurements and a venipuncture to obtain no more than 30 cc blood for A1C, fructosamine and lipid profile.

Assessment 3 with Unblinding/ Debriefing. (week 12- of CPAP/sham-CPAP use). Subjects will be sent the questionnaires, the SenseWear Armband® to use for 7-days before returning for Assessment #3. Subjects will return to the study site with those items, their glucose meter and pedometer. In addition, they will bring their CPAP/sham-CPAP machines and masks. Anthropometric measurements and a venipuncture to obtain fructosamine, A1C, and lipid profile will be done. Prior to being informed of his/her treatment condition, the subjects will be asked to which arm of the study they think they were assigned. The Project Manager/ Study Coordinator and/or PI will debrief the subject, answer any questions and provide a copy of their sleep and laboratory data.

Crossover to Active CPAP. The crossover to active CPAP is important because of two reasons: 1) ethical considerations and 2) and the pilot/feasibility study subjects identified the possibility of eventually being able to try CPAP treatment was a major reason they considered participating in the study. VAPHS subjects who were in either the active and sham-CPAP group will be directed to the Sleep Center at the VAPHS for follow-up care. Non-VAPHS subjects in the sham-CPAP group will be offered the chance to have an actual CPAP titration study, as described above, receive the CPAP education and monitoring, and start CPAP.

Assessment 4. (week 24) All subjects are reassessed as described above; it is the final assessment for those who were initially on active CPAP. We will provide those subjects with a summary of their sleep and laboratory data. Those subjects that crossed-over to active CPAP will continue.

Assessment 5. (wk 36) Those subjects who crossed-over to active CPAP will have their final assessment (after 24 wks of active CPAP) performed as described above. Subject will receive a final debriefing by the Project Manager /Study Coordinator and/or the PI and a copy of their sleep and laboratory data.

Measures to Reduce Attrition. To minimize attrition, in addition to the education/counseling session and telephone calls, we will offer study participants modest monetary compensation for their time. As part of the total compensation, subjects who complete the 12 weeks of CPAP or sham-CPAP when they were blinded to treatment group will receive a $25 bonus if they were adherent to CPAP for at least an average of 4 hours a night. Subjects who were adherent to CPAP for an average of 6 hours a night will receive an additional $25 bonus. Subjects who complete the entire study (24 wks) with active-CPAP will receive a maximum compensation of $270; those on sham-CPAP who then continue to active treatment (36 wks) will receive a total compensation of $300. Subjects will be compensated after designated assessment time-points. Excluded participants will be compensated for activities they complete.

Change in protocol 7.12.2018 (all sites)

- **Assessment 4 will be the final assessment for both Active and Sham. Subjects originally on Sham will be offered 12 weeks of Active treatment, instead of 24 weeks of Active treatment**
- **Assessment 5 is removed from protocol**

- **The maximum compensation for both Active and Sham is $280**

Data Management. Data processing and management will be conducted in the Center for Research and Evaluation (CRE) at the University of Pittsburgh under the supervision of Dr. Sereika, Director of CRE and co-investigator for this project. The CRE also provides support for form design, data entry and verification, programming, and data management as fee-for-service. The CRE supports the design and implementation of paper-and-pencil, computer-based and web-based data collection forms.

The CRE will serve as the data processing center for all data collected. Form design and data management will be conducted in the CRE under the supervision of Dr. Sereika, Director of CRE and co-investigator/statistician for this project. Oracle (version 11*g*, Oracle Corp., Redwood Shores, CA) will be used for data management. Data will be collected in three forms: paper-and-pencil instruments, electronic monitors, and biological values. For paper-and-pencil instruments, Teleform Elite (version 10, Verity, Inc., Sunnyvale, CA), a Windows-based software package for automated data entry/verification, will be used for form design, data entry, and data verification.

For each form, the corresponding Oracle database tables will be initialized for automatic data exportation, and data dictionaries will be created. Following data collection all forms will be thoroughly screened for completeness of response upon receipt and scanned into the database; therefore, we anticipate that there will be very little missing data due to oversights in collection. During verification, erroneous responses will be checked with the source documents and corrected before proceeding with further verification. Using the data dictionaries and data editing programs, final range checking and contingency checking of responses will be accomplished. After this final data cleaning, summary indices and scales will be computed, and the data files for statistical analysis will be created. Data collected using electronic data capture methods (SenseWear Pro Armband®) will be uploaded from the devices to the project computer, interpreted using the software, exported as an ASCII file, and merged with identifying information into the Oracle database. The biological data will be entered in an Excel file at the laboratory then merged with the project's Oracle database. The Oracle database is maintained on an off-site centralized server housed at the Network Operating Center (NOC) of the University of Pittsburgh. The NOC is a secure, high availability University facility equipped with backup power, redundant networking, heating, and cooling, 24-hour staffing, and a data mirror system to create continuous backups.

Data collection at West Virginia University will be performed by the study team with verification and oversight provided by PI, Dr. Stansbury. De-identified data from VAPHS and West Virginia University study participants will be sent to Dr. Chasens' office at the University of Pittsburgh.

C. STATISTICAL ANALYSIS

Data will be analyzed using SAS (version 9.3., SAS Institute, Inc., Cary, NC) to conduct exploratory data analyses, missing data estimation, and repeated measures modeling. Mplus (version 6.12, Muthén & Muthén, Los Angeles, CA) will be used for the fitting of mediational models to explore mechanistic pathways. When screening data, the level of significance will be set to .05 for two-sided hypothesis testing. Although directional hypotheses have been posited for the endpoints associated with the primary aims, a more conservative approach will be adopted and hypothesis testing will be nondirectional. Given the multiple endpoints and time points to be examined for the primary aims, the testwise level of significance will be set at .01 to limit the inflation of type 1 error. Confidence intervals for point estimates will be computed at 99%.

Preliminary Analyses. Detailed exploratory data analyses will first be performed, involving data description and data screening for anomalies (e.g., outliers, nonnormality, etc.). The results from this initial investigation will be used to: 1) describe univariate and bivariate data distributions; 2) identify imbalances between treatment groups and associations between the dependent variables and suspected covariates/confounders); 3) evaluate the amount and patterns of missing data; and 4) check for the violation of statistical assumptions for the planned analyses. Covariates/confounders will be included in models secondarily and their effect on the results of primary predictors/factors will be evaluated. The randomness of missing data will be investigated using available information on subject characteristics to help discern patterns in the missing data, identify the possible covert missing data mechanisms, and inform the choice of the strategies to handle missing data. It is anticipated that the primary reason for data to be missing will be subject attrition. We will closely monitor attrition and conduct logistic regression models via SAS PROC LOGISTIC to compare the characteristics of participants who remained in the study versus those who dropped out to determine if data are missing at random. If the data are missing at random (i.e., not related to the outcome itself), likelihood estimation procedures, such as those used in SAS PROC MIXED, GLIMMIX and NLMIXED as well as Mplus, will produce unbiased estimates while allowing us to retain cases with missing values on the outcome variables. If needed, multiple imputation would be used to impute missing values on the predictor variables. If the data are not ignorably missing, we use pattern mixture or selection modeling to examine data attrition.

Data Analysis Plan for Primary Aim 1. An "intent-to-treat" (ITT) approach will initially be used during data analysis when investigating efficacy of CPAP+DEC compared to sham-CPAP+DEC. All subjects will be included in the data analysis in the groups to which they were randomly assigned, regardless of the adherence to protocol, treatment received, withdrawal or deviation from protocol. Adherence with the assigned protocol, will be monitored throughout the duration of the study. With this ancillary information, the sensitivity of the results under the ITT model will be explored to identify the effects of the amount of intervention received and the deviations in protocol on the efficacy of the interventions. Since the primary endpoint of interest, glycemic control, is assessed repeatedly using two measures, fructosamine and A1C, linear mixed modeling (LMM) with linear contrasts to test the stated hypotheses. A flexible modeling approach, mixed modeling allows for unequally spaced assessments, fixed and time-varying covariates, dependent variables with data that are missing at random, and modeling the covariance/correlation among longitudinal responses. We will consider the baseline value both as an assessment point as well as a possible covariate in analyses. The primary independent variable is the randomized assignment to treatment (CPAP+DEC vs. sham-CPAP+DEC). Fixed and/or time-dependent covariates (including baseline outcome values) may be included in the repeated measures model as indicated secondarily based on the results on the preliminary data analysis to adjust for group imbalances or variables related to the dependent variable. Prior to fitting the repeated measures model, the structure of the estimated covariance matrix for the repeated measures will be carefully examined to determine the appropriate covariance structure. Fit indices will also be used to evaluate the repeated measures models estimated assuming different covariance structures to identify the most appropriate covariance structure. When fitting models, time will be treated as a fixed, repeated within-subjects factor, while treatment assignment will be a fixed, between-subjects factor, with an interaction between time and group. F-tests will be used to test the main and interaction effects included in the model. Individual regression parameters will be computed and reported with their asymptotic standard errors to yield confidence intervals. Sensitivity analyses will be performed to discern the impact of influential cases on results. To test the associated hypothesis (H1), linear contrasts will be specified and estimated when fitting the repeated measures model to compare, relative to baseline values, the CPAP+DEC and sham-CPAP+DEC groups on: 1) the 6-week values of fructosamine and A1C and the 2) 12-week values of fructosamine and A1C. Wald t-statistics will be used to test each linear contrast. Confidence intervals will be obtained for these linear contrasts. Marginal modeling with generalized estimating equations will also be used as it tends to be more robust to misspecification of the covariance structure of repeated assessments and violations in the normality assumption for continuous outcomes.

Analysis Strategy for Aim 2. Using the approach described for Aim 1, repeated measures models will be fitted, and linear contrasts will be estimated to compare 6-week and 12-week values for improvements in diabetes self-management outcomes (retention of information taught during the DEC classes [DKT], improved self-management behaviors [SDSCA], increased physical activity [SenseWare Armband steps], and decreased diabetes-related distress [PAID]) relative to baseline values between subjects on CPAP+DEC and those receiving sham-CPAP+DEC. Generalized linear mixed modeling or nonlinear mixed modeling will be used to analyze longitudinal categorical outcomes should outcome variables need to be categorized for analysis. Along with test statistics and p-values, point and interval estimates will be obtained for linear contrasts.

Analysis Strategy for Aim 3. We will *explore* adherence to CPAP (dose) and specific neuro-behavioral and physiological mechanisms (nighttime sleep, daytime sleepiness, mood, and vigilance during DEC sessions) as possible intervening, or mediator, variables that may mediate the effects of CPAP treatment on glycemic control and diabetes self-management outcomes. Initially, we will fit simple mediational models (predictor, single mediator, single outcome) and estimate whether the effects of CPAP (predictor) on changes in glycemic control and diabetes self-management outcomes are mediated through changes in specific neuro-behavioral and physiological variables (i.e., nighttime sleep, daytime sleepiness, mood, and vigilance during DEC sessions). Standardized parameter estimates of path linkages (with confidence intervals) will be obtained to summarize associations between the exogenous treatment variables, suspected mediators, and distal outcomes, as well as the indirect effect of the treatment group on the targeted outcomes through the suspected mediators and the direct effect of the treatment group on the outcomes. The goodness-of-fit of a model will be assessed using standard summary indices (e.g., RMSEA, CFI) as well as through residual analyses. Depending on the results for testing of individual mediators, we may combine the mediators into a multiple mediator model to develop a more complete picture of these hypothesized mechanisms of action for CPAP.

Analysis Strategy for Aim 4. For this aim we will combine the 6 months of data for the two groups receiving CPAP (including the participants in the delayed treatment group who crossover to CPAP) to *explore* retention of treatment effects and to explore the association between the durability of treatment of OSA (i.e. adherence to CPAP) and 1) sleep

quality [PSQI], 2) daytime sleepiness [ESS]), 3) mood [POMS], 4) diabetes self-management [SDSA, DES-SF, PAID~~,~~ , and 5) glycemic control [fructosamine and A1C] after 24 weeks of active CPAP. For delayed treatment group participants, the initial assessment for this analysis will be their assessments at 12 weeks from study start. Random coefficient modeling will be applied to model changes in sleep quality, daytime sleepiness, mood, diabetes self-management and glycemic control and to associate these changes with objectively measured CPAP adherence via the EncoreAnywhere™. Estimated regression coefficients and confidence intervals will be reported to summarize changes in outcomes over time and their associations with CPAP adherence.

Sample Size Justification. The study sample size of 210 was determined focusing on the testing of hypotheses associated with the primary aims (Hypotheses 1 and 2) and considering the results of the pilot/feasibility study (reported in Approach), the adjustment of the testwise significance level to .01 to limit inflation of type 1 error due the multiple testing of hypotheses at 6- and 12-weeks follow-up for several outcomes, and the anticipated subject attrition during the 12-weeks of follow-up. Regarding Aim 1, our pilot/feasibility study suggests that CPAP improves glycemic control as measured by serum fructosamine (see Table 1). Therefore, we anticipate large effects (in terms of standardized mean differences, d) on the order of d= -0.74 may be detected with 0.80 power with a group sample size of 48 (96 total) when comparing mean changes from baseline to 6 weeks and to 12 weeks in serum fructosamine between CPAP+DEC and sham-CPAP+DEC groups using linear contrasts from a repeated measures model at testwise two-tailed level of significance of .01. Regarding Aim 2, we have observed effect sizes with magnitudes ranging from 0.22 to 1.27 (median effect size of 0.75) for 4-week changes from baseline in physical activity, sleep, vigor, fatigue and vigilance measures (see Table 1). Groups of 84 participants (168 total) will be of sufficient size to detect effect sizes as small as d=0.53 in mean changes from baseline to 6 weeks and to 12 weeks (based on linear contrasts from a repeated measures model) with 0.80 power at testwise two-tailed level of significance of .01. Although efforts will be made to retain study subjects, some subject attrition is possible. Our recent pilot/feasibility study of active-CPAP with a 4-week follow-up in adults with type 2 diabetes demonstrated low attrition of 5%. In the CATNAP study (Weaver et al.) about 10% attrition was observed. To ensure an adequate number of subjects complete the study by conservatively adjusting sample size for 20% attrition, we plan to enroll 210 subjects (105 per group) to have at least 168 subjects (84 per group) complete the study.

Potential Challenges and Strategies. We anticipate two potential problems: 1) management of a large-scale study and 2) loss of blinding by research staff involved in data collection. Our strategies are that Dr. Chasens has the support of a cohesive team of co-investigators who are recognized in their areas of knowledge and have complementary expertise to this project. Our pilot/feasibility study demonstrated that study protocol successfully blinded subjects.[79] We have developed a diagram of study personnel (see Appendix), duties, and blinding status to demonstrate how we plan to maintain blinding. We are aware that reducing subject burden is important. Although we did not have complaints of excessive burden in the pilot study and a 95% retention rate, we have further minimized burden with: 1) home testing of OSA with the ApneaLinkPlus® and 2) consolidating study activity to eliminate a separate discharge/exit evaluation. The two diabetes education sessions are part of standard diabetes care and the one-to-one format is more time efficient than regular group classes. The study sites (UPMC and VAPHS) are accessible by bus and we provide free parking to study participants. We will monitor seasonality as a potential confounder. We have the team and resources in place to implement this vitally significant study that will elucidate the role of sleep disorders as a previously unrecognized but significant barrier to the management of chronic disease.

D. PROTECTION of HUMAN SUBJECTS

Risks to the Subjects

Human Subjects Involvement and Characteristics.

The study sample will be 210 individuals with T2DM recruited from the community or the VAPHS with suspected OSA. Verbal consent will be requested from the potential participants prior to the telephone screening. The telephone screening will use a script to query for inclusion and exclusion criteria. The PI or Project Manager/ Study Coordinator will obtain written informed consent for each study subject at Assessment 1. No study related procedure will be done prior to consenting and giving the subject ample opportunity to ask any questions he/she might have. The clinical protocol has been developed with the focus on maintaining safety and scientific integrity. Potential CPAP/sham-CPAP subjects will be evaluated by a physician or nurse practitioner (not one of the study investigators) to determine that the individual is a safe and appropriate subject for the study. Throughout the data collection period of this protocol we will assess for any adverse events associated with CPAP/sham-CPAP treatment.

Inclusion criteria. Subjects in the final sample who are randomized to CPAP or sham-CPAP will have suboptimal diabetes management (A1C ≥ 6.5%), AHI greater than ≥ 10 (ApneaLinkPlus®); age 18 years and older, and willing to be randomized to CPAP or sham-CPAP.

Exclusion criteria. The exclusion criteria are intended to enhance subjects' safety and ability to complete the study protocol. The table (Table 3) explains the rationale for these exclusions.

Table 3: Rationale for Exclusion Criteria

Exclusion Criteria	Rationale
A1C ≥ 11.0%	These individuals may need changes in diabetes medications
Type 1 or gestational DM	Etiology not associated as directly with OSA as T2DM
Sleep duration < 4 hrs per day	Inadequate sleep may be confounding barrier in addition to OSA
Diabetes meds: change in oral medications or > 10% change in insulin in last 3 months	Improvement in diabetes control from med change may confound results
Acute medical or surgical conditions or hospitalization ≤ 3 months (such as angina, stroke, major surgery, major depression or serious psychiatric conditions)	Subject may be unstable and inappropriate for clinical trial
Previous Dx. of another sleep disorder	Additional sleep disorders may result in continued sleep disturbance
Oxygen or bi-level PAP required	Unable to randomize to sham-CPAP
O2 sat. < 75% for > 25% of the Dx. PSG	Significant hypoxia presents a danger to delay treatment
Prior CPAP or persons in household with CPAP	Increased difficulty in maintaining blinding to CPAP vs sham-CPAP
Cardiovascular events noted during overnight titration sleep study	Significant cardiovascular events presents a danger to delay treatment
Hx. of near-miss or auto accident during last 12 months	Danger of accident from sleepiness
Employed in safety sensitive job (i.e. truck driver or airline pilot)	Danger of accident from sleepiness
Non-ambulatory	Physical activity with walking is aim of study
Regular use of hypnotic or alerting (e. g. modafinil) medications	May interfere with nighttime sleep or daytime alertness
Consumption of alcohol: Men: > 4 drinks a day and more than 14 drinks per week Women: > 3 drinks a day and > 7 drinks per week	May interfere with nighttime sleep or daytime alertness
Claustrophobia to wearing mask	Potentially unable to wear CPAP mask
Unable to speak, read & write English	Not able to perform study tests and participate in the DEC sessions
Pregnant or intend to become pregnant in the next four months (postmenopausal or confirmed not pregnant by a urine pregnancy test)	Changes in respiration, sleep, and energy potentially confound the results
Primary Care Provider request	Subject may be unstable or otherwise inappropriate for clinical trial

Sources of Materials.

All data will be collected solely for the purpose of this study. We will collect the following data for research purposes: Trained staff will perform anthropometric measures, calculate BMI, and obtain blood (venipuncture) to be assayed for A1C, fructosamine, and lipid profile levels for all subjects. We will ask for urine specimens to determine pregnancy in potentially pregnant subjects. We will gauge physical activity and sleep quality/quantity from the SenseWear Armbands® and Sleep/Activity diaries and determine adherence to CPAP from a wireless EncoreAnywhere™ device in the CPAP/sham-CPAP devices that are uploaded to a secure server. Subjects will be told that their adherence to CPAP is being monitored with the devices. We will record vigilance information from the PVT-B and questionnaires that elicit data regarding sleep, sleepiness and mood. We will record the results of the ApneaLinkPlus™ and the overnight PSG that

measures sleep variables including the AHI. We will obtain information from the titration study that records the optimal pressure limit to alleviate episodes of apnea and hypopnea.

Data will be identified only by subjects' assigned unique number and will be stored in locked filing cabinets accessible only to investigators and project staff.

Potential Risks

There are a few potential risks to the proposed protocol. The procedures and standardized tests required by this protocol are all standard assessment techniques that are widely used on patients. The standardized tests employed in the project pose minimal risk to subjects. We will also take precautions to ensure that no patient who is sleepy is permitted to drive home at the end of an assessment visit. Participants will be informed of the danger of driving while sleepy and asked not to drive when experiencing sleepiness. Subjects will be informed that their use of CPAP will be monitored. Except for untreated daytime sleepiness, there are no known risks to the application of the sham-CPAP. As described above, there is no hazard of CO_2 retention or exacerbation of nocturnal symptoms including respiratory events. This placebo has been used in previous research without any serious adverse incident (personal interview C. Kushida, APPLES PI, May 29, 2008) and data from the CATNAP (T. Weaver, Consultant) trial indicates minimal risk to study participants. Subjects will experience side effects associated with the technological interface as they would with active CPAP treatment.

Our consideration of the ethical issues related to the use of the placebo is addressed in that subjects are fully informed that they may be on a sham-device during the consent process. The sleep evaluation and treatment of subjects will be according to clinical guidelines with the exception of subjects treated with the sham-CPAP intervention. Subjects who are assigned to the sham-CPAP will be given the opportunity to participate in a therapeutic use of CPAP at the completion of their study. Subjects may feel boredom or stress in filling out questionnaires and may view study requirements as burdensome. Subjects may have bleeding, bruising, soreness (infrequent; occurs in 1%-10% of people) and fainting or infection at the site of venipuncture (rare; occurs in less than 1%). The *ApneaLink* Plus risks include the potential for the subject to experience nasal mucosa irritation from the cannula (common, occurs in 1-25%) or skin irritation around the nose and or behind the ears from the nasal cannula (rare, occurs in less than 1%). There are no risks associated with becoming entangled in the breathing tube during sleep. The breathing tube is short (21 inches in length) from the recording device to the nose. Mild skin irritation at the site of the finger sensor, similar to what one might experience when taking a bandage off is rare (occurs in less than 1%).

The BodyMedia SenseWear Armband® activity monitor is powered by a rechargeable battery; the chance of a mild electrical shock is very unlikely. The monitor fits around the upper arm and is secured with Velcro. There is the unlikely possibility of a rash or chafing at the site under the armband.

Recruitment and Informed Consent

A record without any identifiers will be kept of all individuals who contacted the study but refused to participate. Individuals not consenting to participate will be asked for the reason for their decision. This reason will be documented in the tracking system. We will read them a statement asking for voluntary oral permission to participate in the telephone screening process. Respondents who do not want to participate in the screening will be thanked and no further questions asked. The questions asked in this screening interview pose no more than minimal risk for the potential participants and are questions that would not require prior consent outside the research context. Those who meet preliminary eligibility criteria will be invited to enroll in the study. Recruitment will be monitored monthly (see Table 4). We will utilize the expertise of Drs. Redline and the involvement of the entire research team of investigators and staff in achieving our recruitment goals.

Table 4: Sample Recruitment Monthly Monitoring

Date				
Total Subjects evaluated				
Subjects randomized				
Men Randomized (month/cumulative)				
Women Randomized (month/cumulative)				
Whites Randomized (month/cumulative)				
Minorities Randomized (month/cumulative)				
Total Randomized Subjects				

Total Goal for Study (to date)				

The PI or Project Manager/Study Coordinator, in accordance with the Institutional Review Board (IRB), will obtain written informed consent for each study subject. Prior to any data collection, we will provide written and oral explanations of the study's purpose, protocol, risks, and benefits. The candidates will have an opportunity to ask questions and then will be asked to sign the form consenting to participate in the study. All advertisements to recruit subjects will be reviewed and approved by the IRB. The study's Steering Committee-(PI, Site PIs and the Co-investigators), as-well as the IRB must agree upon any amendment or revision to the protocol as the trial progresses. One copy of the informed consent form will be given to each subject. One signed copy will be retained in the investigator's study records. At West Virginia University the consent will be scanned into the patient's electronic medical record.

Protection Against Risk - To prevent adverse events this study will follow IRB review and surveillance. The following actions will be taken to protect subjects from risks.

a) Subjects will be given the National Sleep Foundation "Drowsy Driving Sleep Sheet" to inform them of the risks associated with drowsy driving.
b) The consent form indicates that subjects should not drive when sleepy. Subjects are informed they should report any falling asleep while driving events to the Project Manager/ Study Coordinator at the time of the monitoring telephone calls during the intervention.
c) A form called the "Risks of Daytime Sleepiness" will be reviewed with the subject. Questions at the end will be answered to indicate understanding.
d) After the intervention has been initiated, if a subject report falling asleep while driving, their treatment group will be unblinded and the subject will be withdrawn from the study.
e) Questionnaires will be completed in the privacy of the subjects' home; they will be instructed to take rest periods as needed if they find completing the questionnaires as burdensome.
f) Monitoring physical activity with a SenseWear Armband®, having a venipuncture to draw 30cc of blood by trained phlebotomists and responding to questionnaires have only minimal risks to subjects who participate.
g) Procedures are in place to maintain the security and confidentiality of subject data. All paper-based records will be kept in a secure location that is locked and accessible only to personnel involved in the study. The EncoreAnywhere™, a patient compliance management system, is a HIPPA approved, secure web-based password protected program that contains de-identified adherence data. Multiple levels of password protection (i.e., record, file, directory, server, and computer levels) will ensure data security. All study data will be backed up nightly. The finalized datasets along with documentation and their corresponding syntax files for analysis will be stored on the secure centralized server and written to a CD for off-site archival. No subject identifiers other than the subject's assigned unique study identifier will be contained in any of the data files or in any of the subject files that are stored in locked filing cabinets.
h) Sham-CPAP circuits will be inventoried and destroyed after use so that none are used inadvertently by persons other then the subjects randomized to that group.

IRB review and investigator certification:

Permission to conduct the proposed study will be obtained from the University of Pittsburgh's Institutional Review Board. All study personnel will maintain current certification in Research Practice Fundamentals, as mandated by the IRB. The West Virginia University IRB will approve and monitor study activities conducted on the WVU campus. The VAPHS will approve and monitor study activities conducted at the Veterans Administration Pittsburgh Healthcare System.

Potential Benefits of the Proposed Research to the Subjects and Others

There may be a direct benefit to subjects in this study in that all subjects will be provided with two one-on-one DEC sessions and three follow-up phone calls with a diabetes educator. In addition, subjects may learn about sleep apnea and how to increase their usage of CPAP. As detailed below, the study offers significant potential benefit by providing new information about the effect of sleep disorders and related sleepiness on physical activity and outcomes of a DEC program in persons with T2DM. Our findings may result in the development and implementation of behavioral interventions to promote sleep and improve daytime function in persons with T2DM.

Importance of the Knowledge to be Gained

Although CPAP has been shown to improve nighttime sleep and daytime function in persons with OSA, we know of no published study that has examined whether this treatment for OSA improves outcomes of diabetes management. The proposed study will test the hypotheses that treatment of OSA will result in improved glycemic control and diabetes self-management. The knowledge to be gained is important because it is not known whether sleep disorders act as a barrier to learning diabetes self-management, incorporating knowledge of diabetes self-management into lifestyle, or the burden of managing a chronic disease. CPAP treatment of OSA, known to improve nighttime sleep and reduce daytime sleepiness, may also be conducive to increasing the diabetes self-management of persons with T2DM. We will examine if subjects who receive treatment of OSA with active CPAP not only have increased retention of knowledge taught in DSME but also to have increased integration of DEC behavioral lifestyle interventions aimed to increase glycemic control. Given the strong association between OSA and T2DM, the proposed study will provide much-needed information on the effect of CPAP for OSA on diabetes self-management and glycemic control. These potential benefits far outweigh the minimal risks of the study.

Data and Safety Monitoring Plan

We consider subject safety essential. The PI will review reports reflecting data quality, safety, and monitoring as indicated in Table 5 and monitor for potential adverse events and protocol adherence. There will be weekly meetings with the study staff to review the progress of the study. There will be monthly meetings with members of the investigative team to support the study. A Safety Officer who is a physician but independent from the investigative team will be available to monitor and oversee subject safety on an ongoing basis. There will be a telephone meeting between the PIs and Project Managers/ Study Coordinator of the sites (Pittsburgh, VAPHS and West Virginia University) at least every two weeks. All sites will follow their respective IRB policies in reporting AEs/SAEs/UAPs.

Table 5: Data Safety Monitoring, Data Type and Frequency of Review

Data Type	Frequency of Review		
	Site PI, Project Manager and Staff	**Site PI, Co-I, Project Manager, Staff**	**Project Team (Pitt PI and Project Manager), DSMB & Safety Officer**
Subject recruitment, enrollment, retention	Recruitment and enrollment reports weekly; retention rate reports monthly and every 6 months and at the completion of the study	Monthly and as needed informal meetings with Co-investigators. Meeting at least twice yearly o review subject recruitment, enrollment and retention	Recruitment and enrollment reports every 6 months during study, more frequently if recruitment issues arise and warrant it.
Adherence to study protocol for inclusion and exclusion criteria and demographics	Adherence to inclusion and exclusion criteria weekly during recruitment and enrollment phases of study; adherence to demographic criteria every 6 months	Monthly and as needed informal meetings with Co-investigators. Meeting at least twice yearly to review adherence to study protocol	Inclusion and exclusion adherence reports and demographic adherence report every 6 months during study
Adherence of subjects to treatment protocol	Adherence statistics (BodyMedia SenseWear Armband®, Sleep/Activity Diaries, CPAP adherence) monthly & at each scheduled assessment and/or data-collection point, per study protocol; at study completion for each subject	Monthly and as needed informal meetings with Co-investigators. Meeting at least twice a year to review adherence of subjects to treatment protocol	Every 6 months during study
Adverse event rates	Immediate notification and review for each event; quarterly rate reporting	Immediate notification as needed, to review at least twice a year.	Immediate notification and review for each adverse event; review report quarterly
Data coding, entry, and preparation for analysis	Monthly	At least twice a year meeting.	No review needed
Subject complaints	At all project meetings.	As needed in informal meetings with Co-investigators at least twice a year to review.	Every 6 months and as needed
Out-of-range laboratory values (not expected.)	PI will contact subjects who have out-of-range values and recommend their contacting their primary physician. If	As needed informal meetings with Co-investigators. At least twice a year meeting to review.	Every 6 months, the PI will send reports to the Safety Officers and discuss follow-up.

	immediate attention is warranted, with subject's permission, the PI will notify the subject's physician.		

A Data and Safety Monitoring Board (DSMB) was created to review this study. Members consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required. After initial approval and at periodic intervals (to be determined by the committee) during the course of the study, the DSMB responsibilities are to:

1. Review the research protocol, informed consent documents and plans for data and safety monitoring;
2. Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, adverse events, unanticipated problems, performance of the trial sites, and other factors that can affect study outcome;
3. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
4. Review clinical center performance, make recommendations and assist in the resolution of problems reported by the PI;
5. Protect the safety of the study participants;
6. Report on the safety and progress of the study;
7. Make recommendations to the PI, and if required, to the NIDDK concerning continuation, termination or other modifications of the study based on the observed beneficial or adverse effects of the treatment under study;
8. Monitor the confidentiality of the study data and the results of monitoring;
9. Assist the PI by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The DSMB will include experts in clinical trials, diabetes, sleep medicine, and biostatistics. Members will consist of persons independent of the investigators who have no financial, scientific, or other conflict of interest with the study. Written documentation attesting to absence of conflict of interest will be required.

The University of Pittsburgh Office of Clinical Research, Health Sciences will provide the logistical management and support of the DSMB. A safety officer (chairperson) will be identified at the first meeting. This person will be the contact person for serious adverse event reporting. Procedures for this will be discussed at the first meeting.

The first meeting will take place before initiation of the study to discuss the protocol, approve the commencement of the study, and to establish guidelines to monitor the study. The follow-up meeting frequency of the DSMB will be determined during the first meeting. An emergency meeting of the DSMB will be called at any time by the Chairperson should questions of patient safety arise.

The PI will report any adverse events to the University of Pittsburgh IRB and will notify the WVU IRB and the DSMB Chair/Officer. No protocol modification will be instituted without IRB approval.

Unmasking (Unblinding) of Treatment

If there is a serious adverse event, anticipated to be an uncommon occurrence, the PI, Medical Directors, Safety Officer or DSMB will, when necessary for the safety of the participant, unmask treatment group assignment. The administration of the intervention may be discontinued at the patient's request or by the investigator, based on clinical judgment. Participants will be instructed to report any adverse event experienced after treatment without delay.

Protection of Confidentiality

No personal identifiers will be connected with the data. A unique study identification number will be assigned to each participant and a log accessible only to the investigators and key study personnel will link the study identification number to medical record numbers, when applicable. Only appropriate and authorized personnel are able to view, access, and modify study data. Data result (results of ApneaLinkPlus®, titration PSG, and laboratory results) will be sent only to the Primary Care Provider that has been indicated with the subject's permission as noted in their informed consent. No data from questionnaires or other variables will be shared with any other persons. No data on participants' use of CPAP will be provided to any caretaker or company involved in the clinical management of patients or in the provision of equipment for this study.

Each subject in the study will be assigned a unique study code number to be used on all data forms. A list of participant names and code numbers will be maintained separately. Only the investigators and project staff will have access to this information. All personally identifiable information will be kept strictly confidential and in a locked file cabinet.

Evaluation of the Risk / Benefits of the Proposed Research to the Subjects and Others

There is no direct benefit to subjects in this study other than the diabetes education and counseling sessions. The study has minimal risks and the significant potential benefit of the proposed study is the importance of the knowledge to be gained. The proposed study will add to the existing knowledge about the effect of treatment of OSA and 1) diabetes self-management outcomes and 2) glycemic control in persons with T2DM. Potentially, this knowledge will expand our understanding of the effect of sleep disturbances on diabetes self-management which may lead to improved guidelines for screening and treatment of OSA in this population.

Research Study Costs

No procedures that are part of the protocol will be charged to the subject or his/her insurance provider (ApneaLink Plus home sleep study, titration sleep study, CPAP machine).

Research Study Compensation

Research subjects will not be charged for any of the procedures performed for the purpose of this research study. Compensation will be provided for their time for each component of the protocol completed (Table 6). Subjects will need to travel to study sites for their evaluations and the DEC sessions. Each assessment at will take about 1 ½ hours and includes a venipuncture for a blood sample. Questionnaires take approximately 1 hour to complete at home. DEC sessions with CPAP adherence monitoring, the Stanford Sleepiness Scale and PVT-B testing will be also take approximately 1 ½ hr. Assessments and DEC sessions may result in some subjects' potentially missing work. Adherence to CPAP is problematic both in research and clinical practice, adherence to CPAP/sham-CPAP is important for the successful conduct of this study therefore we have a small bonus for those subjects who are adherent for more than 4 hours a night and an addition small bonus who are adherent for an average of 6 or more hours a night. Subjects in the active treatment arm who complete all assessments will receive a maximum of $ 280 (US) and those assigned to the placebo sham-CPAP arm completing all assessments will receive a maximum of $ 310 (US) since this group completes one additional evaluation and 12 weeks of addition participation. There is no reimbursement for the crossover titration study. Persons excluded during the process of the study will receive compensation according to the table. The revised participant incentives are appropriate $7.50/hr for the time involved participating in the study.

Table 6: Research Study Compensation

Activity in Protocol	Compensation	Total Compensation Active CPAP	Total Compensation Sham CPAP
Assessments	$20	$ 80 (Assessments 1, 2, 3 & 4)	$100 (Assessments 1, 2, 3, 4 & 5)
ApneaLinkPlus™ Screening	$10	$10	$10
ApneaLinkPlus™ 2nd Screening **(only if needed)	$10	$10	$10
SenseWear Pro Armband® & Diary	$10/ 7-days	$40 (Assessment 1, 2, 3 & 4)	$50 (Assessments 1, 2, 3, 4 & 5)
History and Physical	$10	$10	$10
Overnight CPAP titration or sham-CPAP titration study	$50	$50	$50
Education Sessions	$10/session	$30	$30
CPAP /sham CPAP adherence	$25 *if* device used ≥4 hours night/ additional $25 *if* device used ≥ 6 hours night)	$50	$50

Totals for CPAP and sham-CPAP participants (maximum)		$280	$310

Subjects will be compensated a maximum amount if fully adherent to the protocol at these time-points: for the active-CPAP group: after Assessment 1 material is returned ($40), after 2nd ApneaLinkPlus™ home sleep study (if appropriate and necessary) ($10), after the history/physical and overnight titration PSG CPAP/sham-CPAP titration study ($60), after the diabetes education sessions (~~3~~ 2) and Assessment 2 ($60), Assessment 3 ($30) plus an additional $25 if the device is used an average of 4 hours per night, plus another $25 if the device is used an average of 6 or more hours per night, and if continuing on to crossover, Assessment 4 ($30). Compensation will occur for the sham-CPAP group: after Assessment 1 material returned ($40), after 2nd ApneaLinkPlus™ home sleep study (if appropriate and necessary) ($10), after the overnight titration PSG CPAP/sham-CPAP titration study ($60), after Assessment 2 ($60), Assessment 3 ($30) plus an additional $25 if the device is used an average of 4 hours per night, plus another $25 if the device is used an average of 6 or more hours per night, and if continuing on to crossover, Assessment 4 ($30), and Assessment 5 ($30). Subjects will be compensated after designated assessment time-points. Excluded participants will be compensated for activities they complete.

University of Pittsburgh Subjects will receive up to $7.50 reimbursement for bus transportation via the WePay System. Parking is provided for those who drive. This is being added as bus costs were included in the NIH approved budget.

UNIVERSITY OF PITTSBURGH COORDINATING CENTER

The University of Pittsburgh PI is responsible for the design and development of the protocol; design and development of case report forms / data collection tools; randomization, and tracking subject enrollment; tracking, reporting, and maintaining serious adverse events and unanticipated problems involving risk to subjects or others, and dissemination of information to all sites; ensuring that the affiliated sites are using the correct version of the IRB protocol and consent documents and maintain IRB approval throughout the conduct of the study; data management, including transmission, storage, and analysis; and recording and distributing devices.

The University of Pittsburgh Coordinating Center will be responsible for providing periodic updates to all sites on subject enrollment, study progress, and any change in the science that potentially impacts the study.

At least every other week there will be a meeting by telephone to update the sites on recruitment and progression of participants. Data will be provided to the University of Pittsburgh DSMB at least every 6 months on subject enrollment and study progress that includes the number of subjects screened, consented, and completing each assessment periods.

The University of Pittsburgh Coordinating Center will monitor, on a periodic basis, the external sites to assess research study progress and compliance with the IRB approved protocol. This will be performed by reviewing site standard operating policies and monitoring data for accuracy received from the sites.

The University of Pittsburgh Coordinating Center will monitor, on a periodic basis, that the external sites are using the correct versions of the IRB, consent documents, and maintaining IRB approval by collecting and maintaining these documents.

Data processing and management for all the sites will be conducted in the Center for Research and Evaluation (CRE) at the University of Pittsburgh under the supervision of Dr. Sereika, Director of CRE and co-investigator for this project.

The University of Pittsburgh Coordinating Center will maintain records of all devices used in the study.

The University of Pittsburgh Coordinating Center will maintain responsibility for the federal reporting of the study to the NIDDK.

The University of Pittsburgh Coordinating Center will be responsible for the training of research staff at each site for all of the research procedures and requirements that are required for that site. This will be done prior to the initiation of the protocol at each of the sites.

INCLUSION OF WOMEN AND MINORITIES

Inclusion of Women

No one will be excluded from the study based on race, gender, HIV status, or ethnicity. Our goal is to enroll approximately 50% women in the study. We were successful in the recruitment of women in the completed pilot/ feasibility study with the sample screened including 55% women and the randomized sample 41% women. We will recruit

a total of 105 women and 105 men to obtain a final sample of 210 subjects who are 18 years of age or older. The ratio of men to women with T2DM is approximately 50:50. We recognize that the risk for OSA is 2.0 to 3.7 times greater in men[126,127] and that potential subjects from the VAPHC are predominantly male. We plan to recruit approximately 60% of the non-VAPHS sample as women and will make special efforts at the VAPHS to target women veterans by focusing recruitment activities to the VA Pittsburgh Healthy Women's Center and to women within the other clinics. In addition, our study advertisements will be designed to recruit women and we will attend health fairs that are specifically directed toward women.

Inclusion of Minorities

Our goal is to have a generalizable sample by enrolling at least 40% minority in the study. We exceeded that number in the completed R21 pilot/feasibility study which included 53% minority subjects screened (41% African American, 3% Asian, 9% Bi-racial [African American and American Indian]) and 45% minority subjects randomized (41% African American and 4% Bi-racial). There remains a paucity of data regarding the risk of OSA by racial group. Redline and colleagues have reported that the risk of OSA for African Americans compared to Whites aged 26-55 is approximately equal (14 vs. 17%). [128] The estimated prevalence of T2DM in African Americans is 2-4 times that of Whites. [129] We will attempt to over-recruit minorities considering the racial distribution in the greater Pittsburgh area (27% African American, 3% Asian-American, <1% American Indian, 1.3%Hispanic). Utilization of the VAPHS site will assist in our recruitment of minorities with a large percentage of their patient population being African American. We will monitor recruitment of minorities and women every month during subject accrual and if we have not met quarterly goals, we will contact the recruitment specialists at the CTSI on methods to increase recruitments within the community and again attend health fairs at churches and community agencies.

If it is necessary to enrich the number of potential participants for a particular gender or ethnic group, Dr. Susan Redline, Professor at Harvard Medical School, will serve as a consultant for the recruitment of women and minority subjects. It is anticipated that the planned actions for retention of all subjects, such as the education session and weekly telephone calls will help retain women and minority subjects. The Data Safety Monitoring Board (DSMB) will closely monitor the recruitment and retention of women and minority participants.

INCLUSION OF CHILDREN

This study includes children older than 18 years because T2DM and OSA are known to affect this age group. At this age there is less difference in the epidemiology, pathogenesis, symptomatology, diagnostic criteria, and treatment of OSA between children and adults.

Neither the intervention nor the outcome measures are appropriate for younger children. Although T2DM has been found to exist among young children (under 18 years), there is no prevalence data on T2DM in this population. Given the significant differences in OSA in the younger pediatric age group (under 18 years) and the OSA of adults, the inclusion of younger children in this clinical trial may not be appropriate. Further, there are issues of study design that preclude the involvement of younger children in this trial. First, the pediatric age group is not of legal age to provide informed consent. This is an issue of great concern given that the use of sham CPAP is potentially dangerous in the pediatric age group. Additionally, participation in this randomized clinical trial would not confer any direct benefit to the individual child enrolled, particularly if the child was randomized to the sham CPAP arm. Another difficulty in children is that tonsillectomy is the primary treatment option for the majority of young children with OSA. In contrast, CPAP is used as first line therapy for only a small minority of young children. Finally, many of the instruments used to measure outcomes in this study (SenseWear Pro Armband®, ESS, POMS) either are not applicable to young children or have not been validated in this under 18 years age group.

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