HYperglycemic Profiles iN Obstructive Sleep Apnea: Effects of PAP Therapy (The HYPNOS Study)

NCT02454153

March 30, 2017

1. Abstract

It is estimated that nearly 25.8 million people in the United States have type 2 diabetes mellitus. Research over the last decade has shown that obstructive sleep apnea (OSA) is a common condition in people with diabetes. Data from a number of different studies show that the prevalence of moderate to severe OSA in diabetics is approximately 50%. Observational and experimental evidence also indicates that intermittent hypoxemia and recurrent arousals in OSA may alter glucose metabolism and worsen glycemic control. However, the impact of treating OSA with positive airway pressure (PAP) therapy on glycemic control is not well defined. Adequately powered randomized clinical trials have yet to be performed to demonstrate whether PAP therapy for OSA in diabetics can improve glycemic control, decrease blood pressure, and reverse endothelial dysfunction. The overarching goal of this study is to determine whether PAP therapy for OSA in diabetics with less than optimal glycemic control leads to improvements in (a) glycosylated hemoglobin (HbA1c); (b) glycemic variability as assessed by self-monitoring of blood glucose and continuous monitoring of glucose; (c) blood pressure; and (d) endothelial function. We propose to conduct a randomized control trial in people with diabetes and moderate to severe OSA who will be randomly assigned for 3 months to PAP therapy along with healthy lifestyle and sleep education (PAP-HLSE) or healthy lifestyle and sleep education (HSLE alone).

2. Objectives (include all primary and secondary objectives)

Primary Objectives: To examine whether treatment of OSA with PAP in diabetics has favorable effects on glycemic control, postprandial hyperglycemia, and glycemic variability.

Secondary Objectives: To assess whether treatment of OSA with PAP in diabetics improves 24-hr blood pressure and endothelial function.

3. Background

Obstructive sleep apnea (OSA) is a chronic condition characterized by repetitive collapse of the upper airway during sleep. The resulting decrease in airflow leads to episodes of intermittent hypoxemia and recurrent arousals that, in turn, trigger a repertoire of physiological events including: (a) activation of the sympathetic nervous system, (b) increase in oxidative stress, (c) alterations in corticotropic function, and (d) release of inflammatory adipocytokines. Collectively, these alterations likely form a synergistic and interactive network that has a negative impact on normal glucose homeostasis. Thus, it is not surprising that an independent association has been demonstrated between OSA, insulin resistance, glucose tolerance, and diabetes.

The prevalence of OSA in diabetes has been a topic of significant research and data published to date show that at least 50% of diabetics have OSA. In the community-based Sleep Heart Health Study, 58% of middleaged and older adults with diabetes were reported to have OSA. Recent findings from Sleep AHEAD study, an ancillary to the Look AHEAD trial, corroborate the high prevalence of OSA in diabetes. Approximately, 53% of the diabetics in the Sleep AHEAD study had moderate to severe OSA (AHI $\geq$ 15 events/h). Given the abundance of data linking OSA to abnormalities in glucose metabolism, a much sought after quest has been to assess the impact of OSA on glycemic control in diabetes and determine whether OSA treatment with continuous positive airway pressure (PAP) therapy can improve hyperglycemia.

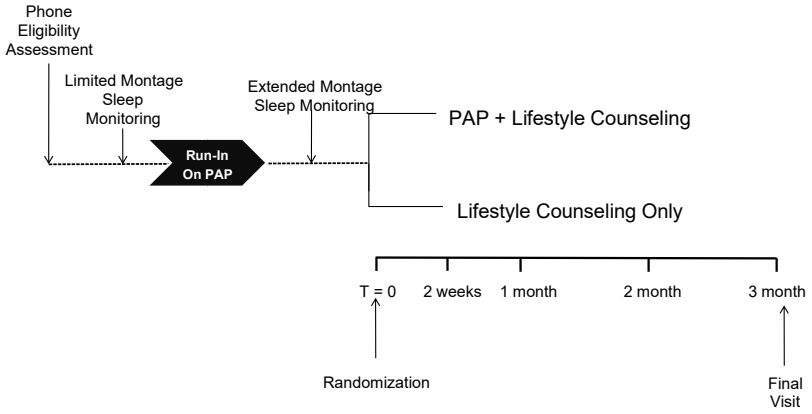
Despite the potential relevance of OSA in glycemic control and diabetes-related comorbidity, only a handful of studies have evaluated whether PAP treatment for OSA in type 2 diabetes is associated with improvements in metabolic function. Of these, only two are randomized clinical trials, with the rest being uncontrolled pre-post assessments after the initiation of PAP therapy. The first randomized clinical trial showed no change in HbA1c in diabetics with PAP therapy. The lack of positive effect in that study could be attributed to several methodological issues including the small study sample (20 PAP treated; 22 controls), the limited duration of follow-up (3 months) and the suboptimal adherence to PAP (3.6 hours/night). Similarly, the second randomized clinical trial also showed that in diabetics PAP therapy for OSA for 3 months has no effect on glycemic control. The lack of a favorable effect of PAP on metabolic control was mostly likely related to the fact that two-thirds of the sample already had good metabolic control at baseline with an HbA1c within the target therapeutic range

(HbA1c < 7.5%). It should come as no surprise that there is a "floor effect" beyond which HbA1c cannot be improved despite optimal treatment of OSA.

Given the paucity of controlled studies, our overarching objective is to conduct a sufficiently robust randomized clinical trial to determine whether PAP treatment of moderate to severe OSA in diabetics with less than optimal glycemic control is associated with improvements in glycemic control, postprandial hyperglycemia, and glycemic variability.

4. Study Procedures

Study Design: Randomized Clinical Trial (PAP therapy + Healthy Lifestyle and Sleep Education [HLSE] versus Healthy Lifestyle and Sleep Education Only). The figure on the following page describes the schema for the study protocol (Note: The diagram does not show every study related procedure).



Study protocol outline:

1. Assess eligibility (via phone) of volunteer participants responding to ads, flyers, or mailings for the study protocol (see inclusion and exclusion criteria below). Based on whether the participant meets the additional criteria, a visit will be scheduled with the study team for informed consent.

2. If a participant does not have any exclusion criteria based on our preliminary screen, a home self-applied monitor (ApneaLink®) will be provided to the participant to record for one night of sleep. These monitors allow for a limited assessment of breathing abnormalities during sleep because only a few channels for physiologic recordings (e.g., oxygen saturation, respiratory effort) are recorded. Analysis of the acquired physiological signals will be used to calculate the oxygen desaturation index (ODI = number of oxygen desaturation per hour of sleep). Only those volunteer participants with an ODI $\geq$ 15 events/hr (i.e., at least moderate OSA) will be considered for further screening. A blood sample (10 ml) for hemoglobin A1c (HbA1c) will also be obtained to exclude those that have good glycemic control (HbA1c < 6.5%).

3. Diabetics with previously untreated OSA will be required to demonstrate that they tolerate wearing the PAP device during sleep. Each participant will be given a PAP device which they can keep for a minimum of 3 nights. The PAP device will need to be used at least 4 hours/night on at least three nights for continued participation. After the PAP Run-In period use and until the extended montage sleep study, the participant will also wear an activity meter (Actigraph) which will allow us to characterize habitual sleep patterns. Because habitual short sleep duration and poor sleep hygiene are known to alter glucose metabolism, we will exclude participants with poor sleep hygiene which will be defined as erratic or inconsistent sleep habits or average sleep duration of < 6 hours.

4. If a participant shows that he/she is able to use the PAP device for the minimal required duration, a

extended-montage sleep study (which includes EEG, EMG, etc.) will be then conducted to characterize sleep quality and breathing abnormalities. If the sleep study shows that the participant does not have moderate to severe OSA, they will not be able to proceed further. We suspect that the number of participants with a positive home sleep test but a negative full-montage sleep study will be minimal. The most likely cause of a positive home sleep test and a negative full-montage study are differences in alcohol use or weight between the two tests. Alcohol can increase the collapsibility of the upper airway during sleep. Thus, if a participant were to drink on one night but not the other study, it is possible to get different ODI values. Moreover, if a modest amount of time passes between the two sleep tests, weight loss is possible, but unlikely. Differences in weight can also result in different ODI values. Thus, to minimize differences in conditions between the two tests, we will request that all participants refrain from any alcohol the night of the evaluations. Furthermore, we will minimize the time window between the two tests to avoid any significant alterations in health habits that could lead to a change in weight.

5. If all of the inclusion/exclusion criteria are satisfied (e.g., OSA defined as an apnea-hypopnea index of at least 15 events/hr with overnight polysomnography and the ability to tolerate PAP), the participant can continue on into the study.

Procedures to be conducted to assess eligibility:

1. **Home Sleep Testing:** The sleep monitor with a limited montage (ApneaLink®) device is a simple selfapplied screening tool for OSA. The ApneaLink® device is capable of monitoring several physiologic signals (i.e. oximetry, nasal cannula) during sleep. These devices are battery powered and provide information on the number of oxygen desaturation episodes during sleep.

2. **Wrist** actigraphy**:** Measurements of activity are commonly used as surrogate markers to infer the duration of average sleep. Actigraphs are simple portable accelerometers that monitor motion/activity data. These units are built as wrist-size watches and are typically worn on the wrist. Eligible participants that agree to participate in the proposed research will be given an actigraph to monitor usual sleep habits. The watch provided can be worn throughout the PAP Run-In period and, if the subject is eligible for the trial, he/she can continue wearing the same watch until the morning of randomization.

3. **Blood Tests:** Measurements of HbA1c will be performed to get a current value.

4. **Extended montage sleep study:** Standard methods for conducting a screening sleep study will be employed. The full montage sleep recording can be performed in the participant's home or in a sleep laboratory environment using similar equipment. These recordings include continuous monitoring of left and right electro-oculograms, surface electroencephalograms, submental and anterior tibialis electromyogram, oronasal airflow, pulse oximetry, thoracic and abdominal movements with piezoelectric gauges, and a modified electrocardiographic lead.

Procedures to be conducted as part of the clinical trial:

1. **Questionnaires:** Basic demographic factors (race, marital status, education, work status, smoking history, alcohol history, and caffeine consumption), sleep-related symptoms, and prevalent medical conditions will be assessed with the Medical History and Sleep Survey. Quality of life will be ascertained using the Medical Outcomes Short-Form 36 (SF-36), Functional Outcomes of Sleep Questionnaire (FOSQ), and the Sleep Apnea Quality of Life Index (SAQLI). To determine a participant's habitual activity level, the Minnesota Leisure Time Physical Activity Questionnaire (PAQ) will be used. Time points for data collection: Before randomization and 3 months.

2. **Anthropometry:** Standard methods will be employed for measurements of weight, height and for neck, waist, and hip circumferences. For example, measurement of neck circumference will be performed by using an inelastic tape that is applied around the neck just below the laryngeal prominence. Waist circumference will be measured at the narrowest part of the torso, at the end of normal expiration. For

obese participants, the smallest horizontal circumference between the ribs and the iliac crest will be measured. Hip circumference will be measured around the buttocks in a horizontal plane at the level of the maximal extension of the buttocks. Time points for data collection: Before randomization and 3 months

3. **Clinic Blood Pressure:** Resting arm blood pressure will be obtained in triplicate using a conventional mercury sphygmomanometer. Cuff size will be determined by measuring the circumference of the upper arm, measured at the midpoint, and identifying the appropriate bladder size from a standard chart. Measurements will be repeated three times and recorded. Time points for data collection: Time points for data collection: Before randomization, 2 weeks, 1 month, 2 months, and 3 months.

4. **24 Hour Blood Pressure:** Participants will be instructed in the use of a 24 hour ambulatory blood pressure monitor. The device consists of a blood pressure cuff that is connected by rubber tubing to a small pressure monitoring device that weighs only 9 oz and fits easily in a shirt pocket. The device will be programmed to measure blood pressure at hourly intervals for the subsequent 24 hours. Time points for data collection: Before randomization and 3 months

5. **Blood Draw:** Venous blood will be collected in vacutainer tubes. Approximately 50 ml of venous blood will be drawn and equally distributed across 6-7 vacutainer tubes with approximately 7 ml in each tube. Serum/plasma will be extracted from venous blood, stored, and assay for the analytes of interest in batches for efficiency. Time points for data collection: Before randomization, 2 weeks, 1 month, 2 months, and 3 months.

6. **Self-Monitoring of Blood Glucose (SMBG):** Each participant will be instructed to record a 7-point SMBG profile (fasting, preprandial/2-hr postprandial at each meal, bedtime) on 3 consecutive days. A commercially available glucometer will be provided by the study along with the glucose measuring strips. The values from the 7-point SMBG will be recorded by the study participant on a paper diary. SMBG profiles are commonly used in the clinical practice for improving glycemic control in diabetics. Time points for data collection: Before randomization and 3 months.

7. **Continuous Glucose Monitoring (CGM):** A continuous glucose monitoring recorder will be used for assessing the 24-hour interstitial glucose profiles. A sterile disposable glucose sensor (Dexcom) will be placed on the skin of the abdomen and another on the area of the triceps (Abbott). Data on interstitial glucose values are automatically transmitted to a wireless monitor every 5 minutes. The CGM system provides continuous measurement of glucose concentration in interstitial fluids over a range of 40 to 400 mg/dL. The CGM recorder will be used for 2 weeks. In clinical practice, CGM is commonly used to assess the effects of meals, exercise, and medication on a patient's glucose levels. Time points for data collection: Before randomization and 3 months.

8. **Endothelial Function Using Peripheral Arterial Tonometry (PAT):** PAT will be measured using the Endo-PAT device (Itamar Medical). This test requires approximately 20 minutes and is performed with participants positioned supine in a quiet environment with dimmed lighting. The participant is asked to remove rings and whether they have allergies to latex. Fingernails are trimmed if overly long. Probes (one-time use only) are then placed on the index finger of each hand. A blood pressure cuff is placed on the non-dominant arm. Following a brief period (5 minutes) of baseline recordings, the cuff is inflated to 60 mmHg above their systolic blood pressure determined earlier (to at least 200 mmHg but not more than 300 mmHg) to occlude blood flow in the arm. The period of occlusion is timed with a stop watch for 5 minutes. At exactly 5 minutes, the pressure is rapidly released and readings taken for a minimum of 5 minutes. Once recording is complete, the probes are removed and discarded. Time points for data collection: Before randomization and 3 months.

9. **Assessment of Body Fat:** Total body fat, a major confounder in the relationship between sleep disturbance and glycemic control, will be obtained using Dual-Energy X-Ray Absorptiometry (DEXA) scan. The

DEXA scan is used to measure body composition in terms of fat and fat-free mass. DEXA systems are used to perform whole-body scans in order to determine the bone and soft tissue composition of the whole body and subregions such as arms, legs, and trunk. The body is partitioned into three segments: bone, fat, and fat-free mass. A total body scan takes 6 minutes and the radiation dose incurred during DEXA scanning is approximately 0.5 millirem, which is a very small dose. DEXA is a simple and safe technique that is routinely performed in clinical care and imposes minimal participant burden. Time points for data collection: Before randomization and 3 months.

10. **Food Diary:** All participants will be required to document their dietary intake for 3 days during the acquisition of the 7-point SMBG and CGM data. Time points for data collection: Before randomization and 3 months.

11. **Home sleep monitoring:** At the 3 month visit, home sleep testing will be repeated (ApneaLink®) and also the actigraph as done during the screening phase.

Procedures to be conducted as part of the interventions:
After completing the required testing, participants will be randomly assigned to one of two treatment groups: Healthy Lifestyle and Sleep Education alone (HLSE) or HLSE plus PAP (HLSE-PAP).

1. **HLSE intervention:** Lifestyle guidelines developed by the American Heart Association and American Diabetes Association for disease prevention and weight loss will be provided to all subjects. Compliance with anti-diabetic medications will be emphasized. In addition, counseling on sleep hygiene using published materials to suggest ways to improve the regularity and duration of sleep, aiming for 7-8 hours of sleep per night. General lifestyle advice relevant for OSA will also be provided, including a recommendation for regular exercise and avoidance of alcohol, particularly near bedtime.

2. **PAP therapy:** This intervention includes OSA treatment with PAP, titrated using a home-based computerized auto-titration protocol. Participants will have an opportunity to try various PAP mask interfaces in order to optimize fit. Verbal and written directions on the use of these materials will be provided, with instructions reinforced after the initial period of PAP titration is completed, and then at scheduled telephone follow-up calls. After each night of use, the recorded data on usage are transmitted from the participant's home to a central computer using a wireless communication feature in the PAP device. The research team will review the transmitted data and judge its acceptability based on usage for at least 4 hours/night for at least 3 nights during the run-in period. After randomization, PAP data will be visually reviewed to identify the optimal pressure, defined as the pressure that eliminates 90% of airflow limited events.

   We recognize that some participants will have less than optimal PAP adherence after enrollment. In participants that use PAP more than 5 h/night during the study, we will provide positive reinforcement regarding their PAP use. In those participants where the use of PAP is poor, we will use Motivational Enhancement Therapy (MET), which is based on the principles of motivational interviewing. Each participant having difficulty with PAP therapy will be asked to provide a subjective assessment of wearing PAP; expected barriers and facilitators of use; and motivation and confidence to use PAP. Issues that are raised with be addressed to improve adherence to PAP.

3. **Telepho`ne calls:** Participants in both groups will receive a phone call from a research team member twice a month after the first month visit. The goal of these calls is to optimize adherence to the lifestyle intervention and also to PAP therapy. Compliance with diabetic medications will be again emphasized. For those randomized to PAP therapy + HLSE, research staff will identify problems that may impact their use of PAP therapy and then implement solutions (e.g., new mask) that could further improve compliance.

Study duration and number of study visits required of research participants.

For the screening portion of the study, each participant will have the following visits: (a) informed consent, (b) PAP run-in phase, and (c) extended-montage sleep study.

After the screening assessments, each participant eligible for randomization will have five visits (randomization, 2 weeks, 1 month, 2 months, and 3 months). To minimize burden, subjects will commence data collection for the CGM and the ambulatory 24 hour blood pressure monitoring at the time of the extended sleep study montage prior to randomization. Finally, because continuous glucose monitoring (CGM) will be conducted for two weeks, participants will exit the study at 3.5 months. During the 2 weeks ofCGM, group assignment will remain as at the time of randomization.

5. Inclusion/Exclusion Criteria

Inclusion Criteria: All participants must be capable of giving informed consent to participate. This study will target type 2 diabetics (age $\geq$ 21 and $\leq$ 75 years) with previously untreated OSA.

Exclusion Criteria: As detailed in the Table below, participants will be excluded if they: (1) have any confounding medical condition, (2) are not willing to be randomized, and (3) are unable to provide consent.

Exclusion Criteria

Inability to consent or commit to the required visits	Occupation as a commercial driver or operator of heavy machinery
HbA1c < 6.5% or > 10.0%	Active substance use
Use of insulin or other injections for diabetes	Untreated thyroid disease
Weight change of 10% in last six months	Pregnancy
Use of oral steroids in the last six months	Any history of seizures or other neurologic disease
Pulmonary disease (i.e., COPD)	Poor sleep hygiene or sleep disorder other than sleep apnea
Renal or hepatic insufficiency	Central sleep apnea
Recent MI or stroke (< 3 months)	Variants of obstructive sleep apnea (e.g., REM-related OSA)
Sleep-related hypoventilation	Excessive subjective sleepiness (Epworth score > 16)
Obesity-hypoventilation syndrome	Participants not suitable for the study based on the clinical judgment
Morbid Obesity	Use of any investigational drug within the past 30 days or participating in another study

6. Drugs/ Substances/ Devices

For the current study, PAP therapy device will be used for treatment for OSA. PAP devices are the standard of care for the management of OSA.

7. Study Statistics

a. Primary outcome variable.
- Glycemic Variability (Continuous Glucose Monitoring: CGM)
- HbA1c
- Self-Monitoring of Blood Glucose (SMBG) Profiles

b. Secondary outcome variables.
- BP, Endothelial Function
  - 24-hr BP profile
  - Endothelial function (Endo-PAT)
- Sleepiness and Quality of Life Assessments
  - Subjective sleepiness (Epworth Sleepiness Scale)
  - Quality of Life (SF-36, SAQLI, FOSQ)

c. Statistical plan including sample size justification and interim data analysis.

Statistical analyses for the primary evaluation of treatment effects will follow the intention-to-treat paradigm, which means that all randomized patients will be included in the treatment group to which they were assigned. Participants who do not have the requisite data for our primary outcomes will be accounted for and compared by assigned group. Participants not able to be included in the intention-totreat analyses will be compared to those who are included with respect to demographic and other characteristics. Periodic descriptive summaries of data will be performed to monitor for adverse events and to improve data quality by identifying and investigating outliers in observed measurements.

The primary outcomes for the trial are changes from baseline to 3 months in HbA1c and postprandial hyperglycemia (□=post-preprandial glucose). Initial analyses will tabulate demographic and baseline characteristics of the participants by randomization group. $□^2$-tests and one-way ANOVA will be used to compare groups on these characteristics. If differences in some characteristics are observed, even though not statistically significant, these variables will be considered for inclusion in regression models assessing our outcomes. The analytical approach will consist of using mixed model linear regression of the change measure (e.g., □HbA1c or improvement in postprandial increment) at 3 months with an indicator variable for the fixed effect for treatment group and baseline value of the measure and adjustment for correlation between baseline and follow-up measures. Additional covariates (e.g., baseline weight and body fat, weight change, sleep duration, activity levels, caloric intake) will be included in the model particularly if the randomization results in serious imbalances in a covariate across treatment groups. More powerful, mixed model repeated measures analyses will also be done using all available longitudinal data on HbA1c and average postprandial-preprandial (□) glucose values including rate of change from baseline. The purpose of these analyses is to examine whether the trajectories of our dependent variables vary over time based on the assigned group.

The secondary outcomes include change in: (1) CGM-derived mean glucose values; (2) systolic, diastolic and mean daytime and nighttime BP; (3) heart rate variability derived indices of sympathovagal balance; (4) endothelial function (Endo-PAT derived reactive hyperemia index); (5) markers of oxidative stress (e.g., oxidized LDL); (6) lipid abnormalities (e.g., LDL, HDL, triglycerides); (7) myocardial injury (troponin-I); and (8) renal injury (urinary albumin and creatinine). All analyses for our secondary outcomes will be done under the intention to treat principle. Initial analyses will tabulate baseline characteristics of participants by randomization group. For our continuous outcomes, we will use multivariable regression and mixed model repeated measures analyses as done for the primary outcomes.

Sample Size Determination:
Sample size was calculated based on the magnitude of anticipated improvement in our primary outcome (e.g., standard deviation [SD] of Dexcom CGM glucose values). The primary assumption for determining sample size was an expected mean decrease in SD of CGM glucose values of 3.3 mg/dl (SD: 6.9 mg/dl) with PAP therapy with no expected change in the control group. Assuming a type 1 error and a power of 90%, a sample size of 92 participants would be needed in each arm (total N =184). To account for modest dropout (~10%), the enrollment goal was 102 participants in PAP therapy arm and 102 participants in the control arm. A total sample size of 184 participants would also allow the study to detect a mean HbA1c difference of 0.36% between the two groups. Enrollment began in December 2014 and ended in December 2019 with a final sample size of 186 participants. In response to the COVID19 pandemic, all clinical research activities ended in early March 2020.

d. Early stopping rules.

Not applicable.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Questionnaires: There are no risks to completing the study questionnaires.
Actigraphy: There are no risks associated with wearing an Actigraph.
Overnight sleep study: There are no major risks with a sleep study. Rarely, some individuals may experience minor redness or irritation at the site of the monitoring electrodes.
DEXA: This is a widely used test in clinical care for bone density and can also provide measures of body composition. With the newer generation instrument, a whole body scan takes about 6 minutes and the total effective dose of radiation to the participant is 1 millirem. This amount of radiation is significantly less than that from a standard PA + lateral chest x-ray series. Only nonpregnant participants will be enrolled in the protocol.
Anthropometry: There are no risks with anthropometric measurements.
EndoPAT: Risks associated with this test are minor and include numbness, tingling or slight discomfort at the site of the blood pressure cuff during and post inflation. These sensations are temporary and resolve within 2-3 minutes.
Electrocardiogram and Blood Pressure: These are routinely performed in clinical care and have no risks.
Blood Draw: Risks include infection, hematoma, and minor pain at the puncture sites.
PAP Treatment: In our experience with PAP therapy over 20 years, we have not had any serious complications resulting from positive nasal pressure administration in the clinical range ($\leq$ 20 cmH_20). Minor side effects include feeling bloated, nasal mucosal dryness, discomfort from the nasal mask, and irritation of area around the nose where the mask makes contact with the face. Some patients can also develop sinus infections but these are rare and are easily treated.

b. Steps taken to minimize the risks.

Veni-Puncture: Discomfort, bruise formation, and infection will be minimized by use of sterile supplies and aseptic technique by trained personnel. Any complications will be evaluated by a physician. In the case of an adverse event, the patient will be referred to the appropriate clinical specialist, either outpatient or inpatient for care. Adverse events related to the study procedures will be reported to the IRB. All other procedures (questionnaires, blood pressure monitoring, activity monitoring, SMBG, CGM, sleep study, PAP therapy) are of no more than minimal risk.

c. Adverse events.

Any adverse events, unanticipated problems or study deviations will be reported to the IRB by the primary investigator. A DSMP plan has been drafted and included in the eIRB application

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Breach of confidentiality would result in unauthorized individuals having access to information about the participant's medical history. Several different measures will be undertaken to protect participant confidentiality. Paper files will be in locked file cabinets. Access to any computerized information will be restricted to the study investigators or associated staff. Participant data will be stored with unique identifiers and will be password protected. Encryption algorithms that can only be reversed with password access will be implemented. All computers will require log on passwords.