# Impact of a Novel Sleep Apnea Management Group Intervention on Positive Airway Pressure Adherence: A Randomized Controlled Trial

**NCT03835702**

**Study Protocol and Statistical Analysis Plan**

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## Introduction

**SPECIFIC AIMS:** Obstructive Sleep Apnea (OSA) affects ~10-15% of the adult population in the United States and when present to a moderate to severe degree is associated not only with decrements in quality of life, but also increased cardiovascular risk and a 2-fold increase in mortality. Positive Airway Pressure (PAP) is the mainstay treatment for OSA. Suboptimal PAP adherence (only 40-70% of patients are adherent) poses a continued substantial threat limiting ability to mitigate the negative consequences of untreated OSA. PAP adherence is therefore an essential focus of clinical management that requires persistent monitoring and practical problem solving, as too many patients derive suboptimal medical and psychological benefits due to their insufficient use of this proven therapy. Indeed, even clinical trials have demonstrated suboptimal PAP adherence despite intense observation thereby limiting ability to effectively interpret results. There is evidence that frequent patient contact to troubleshoot seemingly mundane problems contributes to improved adherence. Preliminary evidence demonstrates benefit through attendance of a group clinic designed to encourage patient adherence with PAP therapy as it provides a simple and effective means of improving treatment of OSA, however randomized controlled trials, are sorely needed to extend this evidence and inform patient care.

## Background and Significance

The Sleep Apnea Management Clinic (SAM) is a novel group clinic created and embedded in the Cleveland Clinic (CC) System to address challenges in positive airway pressure (PAP) management by promoting adherence via providing access to problem-solving of PAP therapy issues. This innovative and interactive format allows patients with common problems and needs to have direct access to sleep medicine providers, sleep nurse practitioners, sleep nurses and/or durable medical equipment (DME) representatives all in one room in order to receive the most efficient service. While there are limited data focused on examining group clinics for PAP education, there are scant data that have assessed PAP adherence and its barriers in a group setting. Our team has played an integral role in the design, development, and establishment of the SAM Clinic initiative and has extensive experience in its management and operations. We propose a randomized controlled trial, involving 83 patients in SAM clinic and 83 patients in usual care and compare PAP adherence, patient reported outcomes and PAP barriers. Expected results will be of high impact given ability to identify and inform future treatment approaches for management of OSA with PAP and identify key outcomes for clinical trials. In doing so, this line of investigation will likely have a significant clinical impact to enhance PAP adherence and ameliorate adverse clinical outcomes associated with OSA patient populations across systems of care.

## Specific Aims

**SA 1. To examine the impact of the sleep apnea management (SAM) group-based intervention on Positive Airway Pressure (PAP) adherence (primary outcome) compared to a patient group managed by physicians (patients who follow usual care and are receptive to the SAM Clinic but do not participate in a SAM group) on changes from baseline to 1 and 3 months in those with moderate to severe OSA with suboptimal PAP adherence.**

*Hypothesis 1: We hypothesize that the SAM clinic intervention will result in improved PAP adherence versus usual care.*

**SA 2. To examine and compare changes in patient reported outcomes (PROs, i.e. daytime sleepiness, quality of life measures, and depressive symptoms) between the SAM Clinic and the usual care arms from baseline to 1 and 3 months in those with moderate to severe OSA with suboptimal PAP adherence. To examine the correlation between changes in PROs to changes in PAP adherence at each time point (secondary analyses).**

*We hypothesize that greater improvement in PROs will be noted with the SAM clinic intervention compared to usual care.*

**SA 3. To examine the impact of the SAM Clinic on changes in barriers to PAP adherence compared to usual care from baseline contact to 3 months in those with moderate to severe OSA with suboptimal PAP adherence.**

*We hypothesize that the SAM Clinic intervention will be able to address PAP barriers more effectively compared to usual care.*

**PRELIMINARY DATA:**

**A. Impact of the SAM Clinic on PROs and PAP barriers (presented at SLEEP 2018)**

**Table 1: PRO Changes following SAM treatment in OSA patients**

| | ESS | | FSS | |
|---|---|---|---|---|
| | Change (95% CI) | p-value | Change (95% CI) | p-value |
| Post-SAM | -1.52 (95% CI -2.10, -0.93) | <0.001 | -2.88 (95% CI -4.73, -1.03) | <0.001 |

A.1 *Changes in PROs*: We analyzed changes in the Epworth Sleepiness Scale (ESS) and the Fatigue Severity Scale (FSS) by capitalizing on the integration of the CC Knowledge Program (electronic PRO data collection platform, described in more detail below) with the electronic medical record, before and after SAM Clinic (180 days), in 235 patients. Table 1 demonstrates statistically significant improvements in ESS and FSS, suggesting additional benefits of the SAM Clinic on patients already on PAP therapy.

A.2 *Changes in Barriers:* We examined the impact of the SAM Clinic on PAP barriers in 21 patients and noted complete resolution of air leak (n=7), mask claustrophobia (n=6), and aerophagia (n=3). Mask-fitting issues were resolved in 10/11 patients, pressure intolerance was resolved in 9/10, and mouth dryness was resolved in 10/14 patients ($p<0.05$ for all except aerophagia).

**B. Data Highlighting the Impact of PAP on PROs in Sleep-Disordered Breathing (SDB)**

*B.1 Changes in PROs with PAP in patients with hypertension and resistant hypertension in a clinical population of SDB*: We examined improvements in PROs in 894 patients with PAP treatment for SDB in the hypertension and resistant hypertension population, which is an understudied area. Table 2 demonstrates the improvement in sleepiness, depressive symptoms and fatigue in both hypertension and resistant hypertension

**Table 2: PRO Changes following PAP treatment in SDB**

| | Epworth Sleepiness Score | | Patient Health Questionnaire-9 | | Fatigue Severity Scale | |
|---|---|---|---|---|---|---|
| | Change (95% CI) | p-value | Change (95% CI) | p-value | Change (95% CI) | p-value |
| Post-PAP | -2.09 (-2.37, -1.82) | <0.001 | -1.91 (-2.25, -1.56) | <0.001 | -4.06 (-4.89, -3.22) | <0.001 |

*B.2 Importance of PAP adherence in improving quality of life in patients with SDB*: In alignment with AASM Quality initiatives, we examined changes in Quality of Life (Qol) measures, including Functional Outcomes of Sleep questionnaires (FOSQ) and European Quality of Life (EQ-5D), in ~2100 patients with SDB using PAP. We found that PAP-adherent patients had greater improvements in FOSQ and EQ-5D scores after excluding those with normal Qol (figure 1). Socioeconomic status and age group were significant effect modifiers. *This study highlights the importance of PAP adherence in improving Qol measures toclinically*

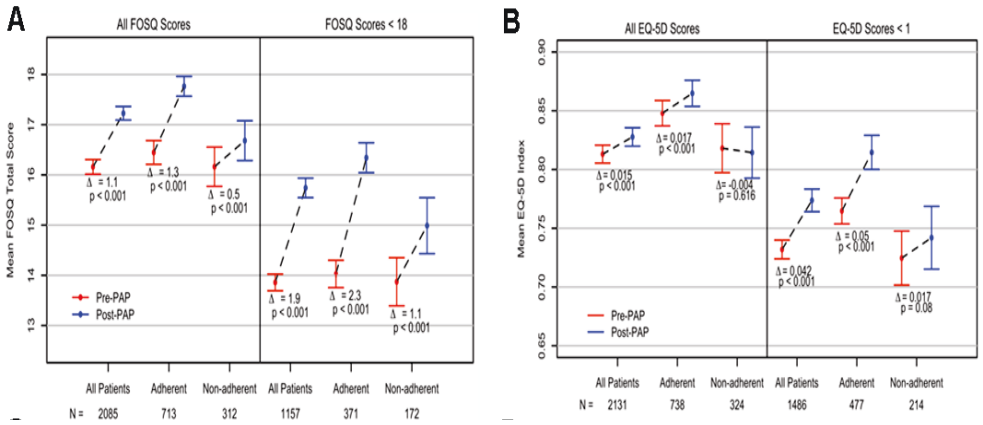


*Figure 1*

*significant degree.*

**Study Design**

**METHODS, INCLUDING EVALUATION METHODOLOGY AND DATA ANALYSIS PLAN**

**Recruitment Strategy:** Trained personnel who have completed the necessary certification for human subject research will screen a patient list of those prescribed with new PAP within 2-4 weeks by providers will be obtained weekly from the Cleveland Clinic Durable Medical Equipment (DME) company. PAP adherence will be ascertained using Encore/My air software®. Patients with suboptimal adherence, defined by the Center of Medicare and Medicaid criteria (≤70 % usage and ≤4 hours of average daily PAP usage) will be identified. The referring providers will be contacted via email/phone/staff message to explain the study protocol and to obtain permission for each patient to be contacted to participate in the study. After obtaining permission from the referring provider, an introduction letter will be sent and the purpose of the research will be explained and a copy of the consent will be mailed to the subject with self-addressed stamped envelopes. The recruiter will then call the patient to review the consent and answer any questions. The participant may request an in-person consenting process, which the recruiter will accommodate. After the signed consent is returned to the recruiter, they will sign as witness and document.

**A written waiver of consent will be requested (according to 45 CFR46.117) to collect and review health information about prospective subjects prior to obtaining written informed consent.** The research involves no more than minimal risk. The waiver will not adversely affect the rights and welfare of the subjects and the research could not be conducted without the waiver because the health information collected is necessary to ascertain which subjects are eligible to participate in the study.

This is a request for partial waiver of HIPAA authorization" to collect health information" from medical records of identified by Cleveland Clinic Durable Medical Equipment (DME) company by Medical Record Number. This will be done by accessing each potentially eligible patient's electronic chart only once in order to review the most recent note from the patient's physician. Information viewed will be used by the study recruiter to check yes or no on the study inclusion and exclusion criteria form with no recording of specific results being made. These forms are de-identified with only the study id listed. No printouts from the Portal will be made. Review of the chart should take no more than 5 minutes per patient. Once a person has been identified as eligible to participate in the study, they will be a recruitment letter introducing the study along with a copy of the consent. All hard copies of this health information will be destroyed about all patients who do not meet study criteria and those who decline participation. All personal health information collected and retained on site prior to obtaining written authorization will be de-linked from identifying personal information. Also, if written authorization is not obtained within 90 days of patients who have agreed to participate in the study, their health information will be destroyed.

**Eligibility criteria:** Inclusion Criteria: 1) ≥18 years old 2) Moderate to severe OSA (apnea hypopnea index (AHI), respiratory disturbance index (RDI), Respiratory Event Index (REI)≥5 events/hr) on polysomnogram (PSG) or home sleep apnea testing (HSAT) 3) Followed by non-sleep and sleep providers for OSA 4) New PAP set up < 1 month 5) Sub-optimal PAP adherence by objective PAP adherence data (≤70 % usage and ≤4 hours of average PAP usage) Exclusion criteria: 1) Central sleep apnea (≥50% apneas are central) and/or presence of Cheyne-Stokes breathing 2) Pregnant women 3) Patients on supplemental oxygen 4) Patients not able to attend SAM clinic 5) Inability to provide informed consent

**Randomization:** Patients will be randomized 1:1 to SAM clinic/sleep hygiene or usual care/sleep hygiene (care by non-sleep providers) using a blocked randomization that stratifies patients based on OSA severity (AHI, RDI, REI 5-14.9, 15-29.9 vs. AHI, RDI, REI >30+). Random assignments to the three arms will be made

with the use of a randomization database in REDcap.

**Study Protocol:** . All data from PAP devices set up by CCDME will be downloaded via wireless communication or smartcard. PAP adherence will be monitored by the research coordinator before randomization (randomized to SAM Clinic or usual care with their provider) and after 1 and 3 month of either intervention. A sample size of approximately 83 subjects is estimated in each group over a period of 2 years (total n=166). SAM clinic appointment will be offered within 1-2 weeks of patient consent and randomization into that group. Both groups will be provided with PAP barriers questionnaires which will be administered in "yes/no" format focused upon specific mask issues (air leak, irritation, fitting problems, type of mask) and other issues (nasal congestion, claustrophobia etc.) and the same questionnaires will be instituted in both the groups at the 1- and 3-month follow-up through the email using redcap platform. See Figure 2 for the flow diagram of the study.

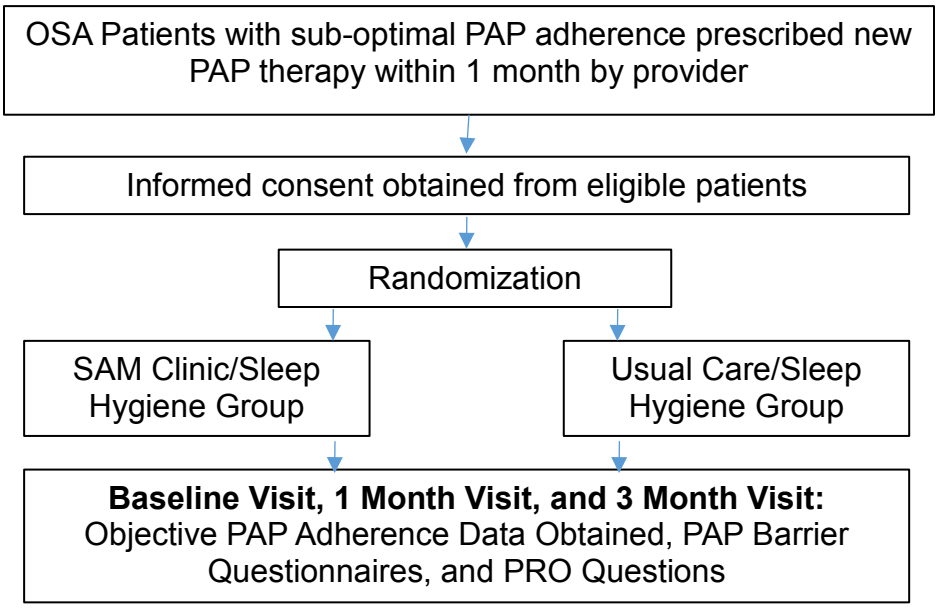


**Figure 2: Flow Diagram of Study**

**Sleep Hygiene Education:** A research coordinator will provide both the arms with sleep hygiene education material at baseline that entails regularization of sleep wake schedule, stimulus control education, adequate amount of sleep and comfortable environment conducive to sleep (by mail).

**SAM clinic Intervention:** See Figure 3 for depiction of SAM clinic visit process. Typically 8-10 patients are scheduled in SAM clinic, during which a sleep provider led team comprised of either a sleep clinician or sleep nurse practitioner along with DME representative(s). Each session begins with a discussion about OSA and PAP. The provider interacts with each patient personally. This occurs on weekly basis at main and other selected regional locations of CC. Various modes of trouble shooting of PAP related issues are tailored to solve PAP adherence issues including mask complaints, nasal issues, pressure intolerance, anxiety, and other related barriers to PAP adherence. **Different interface masks might be provided during the visit depending on the clinical situation (e.g those with claustrophobia will be given nasal pillows)**. When the provider is seeing patients individually other patients have the opportunity to interact and offer informal interpersonal support to other participants in dealing with similar PAP related issues. The provider makes an individualized follow-up plan for each patient, which may include another SAM visit or referral back to the non-sleep provider.

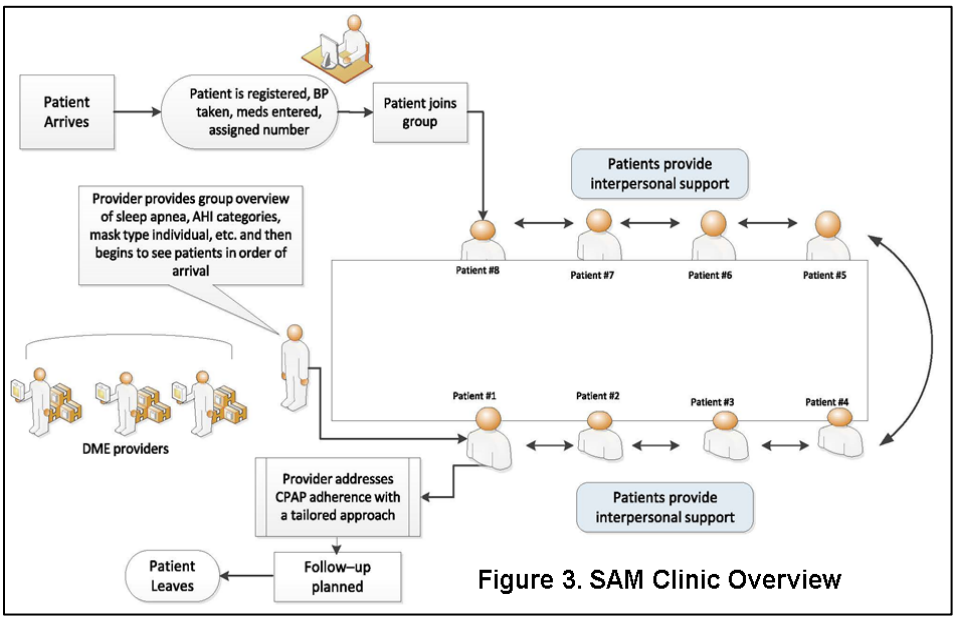

Figure 3. SAM Clinic Overview

**Usual Care:** The control arm will receive usual routine care. Patients will follow-up only with their provider for the monitoring of PAP adherence issues. The follow up visit is usually scheduled1-3 months of the PAP set up and further follow up is contingent upon the clinical scenario of the patient. The usual arm care patients will be recommended to make a follow up appointment with their provider by the research coordinator, if not already scheduled.

**Data Collection:** Data related to PAP barrier questionnaire, PAP adherence, BAS-FS personality index, physiological measurements, PROs (mentioned below) will be collected and entered into the REDcap database of Cleveland Clinic (secured database).

**Procedures:** The RedCap program is a scalable electronic platform to systematically collect patient-reported data through a mobile ready web-based data collection system. Invitation(s) to complete questionnaires will be sent to patients' email with a link to PAP barrier questionnaire and PROs. Enrolled patients can complete these remotely at pre-specified time-points (within a week of enrollment) that are independent from a clinical encounter. The Redcap sends automated reminders and collects management and performance statistics. When each question is completed, real-time data is captured by the RedCap data warehouse.

**PRO Questionnaires:** Epworth Sleepiness Scale (ESS) is an 8-item questionnaire and the most widely used tool for measuring subjective sleepiness. An ESS of ≥10 indicate daytime sleepiness
Patient Health Questionnaire-9 (PHQ-9) is a 9-item depression scale that provides psychometric measurement of depression. A score of >10 indicate moderate to severe depression.
Promis Global Health is a 10-item questionnaire measuring patient reported health status for physical, mental, and social well-being.
Promis Sleep Related Impairment is an 8 item questionnaire used to identify problems in sleep that affect overall quality of sleep.
Promis Fatigue is an 8 item questionnaire that evaluates self-reported symptoms tiredness that affect daily activities and functioning.
Promis Anxiety is a 4-item questionnaire to evaluate anxiety.

**Data Analysis Plan:** Patients will be randomized 1:1 to the two treatment groups using a blocked randomization that stratifies patients based on OSA severity (AHI, RDI, REI 5-15 vs.15-30, 30+). Blocks will be of random size blinded from study investigators. Only the intent-to-treat population will be included in primary analyses, while secondary analyses will be performed in the per-protocol population defined by participation in the SAM Clinic for the treated group versus usual care patients. Linear and non-linear mixed effect models will be used to compare groups for changes in PAP adherence (primary endpoint), PROs, and barriers over time. In these models, group by time interactions will be used to evaluate trend differences between groups, and mean differences primarily at 3 months and secondarily at 1 month. The use of mixed effect models will account for loss to follow-up under the assumption that such dropout is missing at random, though this assumption will be evaluated graphically. If data are missing not at random, pattern mixture models will be further explored to evaluate group differences. Analyses will be performed assuming an overall significance level of 0.05, and comparisons of mean differences at 1 and 3 months will each use a 0.05 significance level. Statistical support will be provided by a biostatistician within the Cleveland Clinic Department of Quantitative Health Sciences for this project.

**Sample Size:** Sample size calculations were performed based on detecting mean differences in PAP adherence at 1 and 3 months. In this study, patients undergoing motivational enhancement (ME) showed an average PAP adherence of 264 minutes (SD: 174) as compared to average PAP adherence of 198 (SD: 168) among those without ME. Given the overall paucity of data addressing PAP adherence in a group setting-we utilized this data from RCT with ME given the similarities in approach. If we assume a similar effect size, and assume that average adherence will be log-normally distributed with a coefficient of variation of 0.65, there will be 80% power to detect an increase of 33% in the mean average nightly PAP adherence with 67 patients per group. Allowing for non-participation and non-compliance rates of 10% in each group, a total of 83 patients per group will be enrolled, the adjustment described by Lachin. This sample size will also provide similar power to detect moderate effect size differences between study groups on PROs, even allowing for dropout on these measures of up to 20% on these measures. Power calculations were performed using SAS software (version 9.4; Cary, NC) and assumed use of a two-sided test with significance levels of 0.05.

**Limitations/Pitfalls and Alternative Strategies:** Since this is a comparative study comparing the effectiveness of SAM clinic to usual standard of care by providers, there are inherent limitations to such a design. There is a possibility of cross over for the patients. We have accounted for possible cross-contamination in the statistical design by increasing the sample size. Patient without email access will be sent paper format of questionnaire. If recruitment become a challenge, will target recruitment efforts in primary care clinics. This study may not be able to shed the light on effectiveness specific mechanisms of SAM clinic intervention e.g. group component vs sleep provider interaction or more. Further research will be needed to investigate it.

**Adverse Event Reporting:** Reporting of adverse events will follow standard reporting guidelines. Each event will be classified according to its severity, whether it was expected or unexpected, and its likelihood of relatedness to the study and reviewed by the study medical monitor, Colleen Lance.

**Consent:** Consent forms will explain in a lay persons' terminology the nature of all procedures. It will be stressed that participation is voluntary. The research assistant and PI will be available to answer questions. All activities will be compliant with local IRB and HIPPA guidelines, such as obtaining physician permission to initiate contact, destroying all pre-screening forms, and obtaining verbal permission, as appropriate for phone interviews. At the beginning of the study, and then periodically, any IRB, HIPAA or privacy requirements that may be in effect at that time also will be checked to assure that plans are compliant with current rules.

Once a person has been identified as eligible to participate in the study, written consent and HIPAA authorization will be obtained. All hard copies of this health information will be destroyed about all patient who do not meet study criteria and those who decline participation. All personal health information collected and retained on site prior to obtaining written authorization will be de-linked from identifying personal information. Also, if written authorization is not obtained within 90 days of patient who have agreed to participate in the study, their health information will be destroyed.

**Potential Benefits:** Participants with sub-optimal adherence may benefit from early recognition. Participants may also benefit sleep hygiene education to improve over sleep.

Participants will receive a monetary compensation of $50 after completing all necessary study visits at the end of 3 months. This payment bay be considered taxable income by the IRS. The participant will be issued a 1099-Misc form only if payment exceeds $600 from all studies in which they are participating in a fiscal year.

**Dissemination Plan:** The study will begin in January 2019 (Table 3 shows timeline)

1. July 2019- complete recruitment of 16 patients in each arm. Manuscript preparation "Rationale for the development of randomized controlled trial for sleep apnea management clinic to assess the PAP adherence".
2. June 2020- cross sectional analyses will be performed to understand the subject characteristics of participants, data analyzed will be used to submit abstract (and manuscript preparation) to national SLEEP Meeting "Subject characteristics of patients presenting in Sleep apnea management group clinic in a randomized controlled trial"
3. July 2020- complete recruitment
4. Dec 2020- Analyze final data; we will submit an abstract to the 2021 Annual SLEEP meeting and utilize data to prepare multiple publications. Primary manuscript on "Impact of a Novel Sleep Apnea Management Group Intervention on Positive Airway Pressure Adherence: A Randomized Controlled Trial". We estimate that there will be ~30% increase in PAP adherence in SAM group compared to usual arm. We also estimate significant improvement in PROs. Secondary manuscripts prepared for peer-reviewed journals will focus on Impact of Sleep Apnea Management Group on patient reported outcomes: "Findings from a randomized controlled trial and Effectiveness of Sleep Apnea management group clinic on Barriers to Continuous positive pressure adherence".

**SIGNIFICANCE OF THIS STUDY:** The proposed work provides a high impact opportunity and addresses two of the proposed research domains including 1. Assessment of barriers of PAP adherence and 2. PAP adherence and PROs managed by sleep providers in a novel group clinic setting of SAM group clinic and comparison with a group managed by providers. The data generated from this proposal will provide effect sizes necessary to inform multi center randomized clinical services research trials. Such an endeavor to research service configuration would be transformative for understanding how PAP treatment can be extended to larger populations of patients.. In doing so, this line of investigation will likely have a significant clinical impact to enhance PAP adherence and ameliorate adverse clinical outcomes associated with OSA patient populations across systems of care. The success of the project will lay in the foundation as a model of effective care provided in group clinics in those with addressable issues with PAP adherence.

**Table 3: A Timeline for The Conduct of the Project**

| Calendar Year | 2019 | | | | 2020 | | | | 2021 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Quarter | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 | 1 | 2 |
| Hiring, refining protocol, Personnel training, IRB Approval, Establishment of recruitment strategies | | | | | | | | | | |
| Recruitment | | | | | | | | | | |
| Anticipated accrual numbers in each arm | | 16 | 16 | 17 | 17 | 17 | | | | |
| Follow up numbers | | | 16 | 16 | 17 | 17 | 17 | | | |
| Data Analysis | | | | | | | | | | |
| Abstracts and Manuscript Preparation | | | | | | | | | | |
| Grant Writing | | | | | | | | | | |

**SAMPAP Study Timeline (Recruitment to Study Completion)**

Day 0

- Patient initiates PAP

Week 2

- Initial eligibility check
- Letter sent to referring provider

Week 3

- Letter/consent sent to patient

Week 4

- Recheck compliance eligibility
- Eligibility confirmed over phone
- Consent completed over phone

Week 4-8 (Baseline)

- Signed Consent received
- Randomization
- Schedule SAM clinic visit if necessary
- Baseline REDCap forms completed
- Baseline patient survey sent and returned
- SAM clinic (if randomized as such)

Week 8-12 (1mo)

- 1mo patient survey sent and returned

Week 16-20 (3mo)

- 3mo patient survey sent and returned
- Stipend issued

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