Cover Page

Protocol Title: Reducing heart failure re-admissions by enhancing sleep apnea treatment adherence

December 1, 2018

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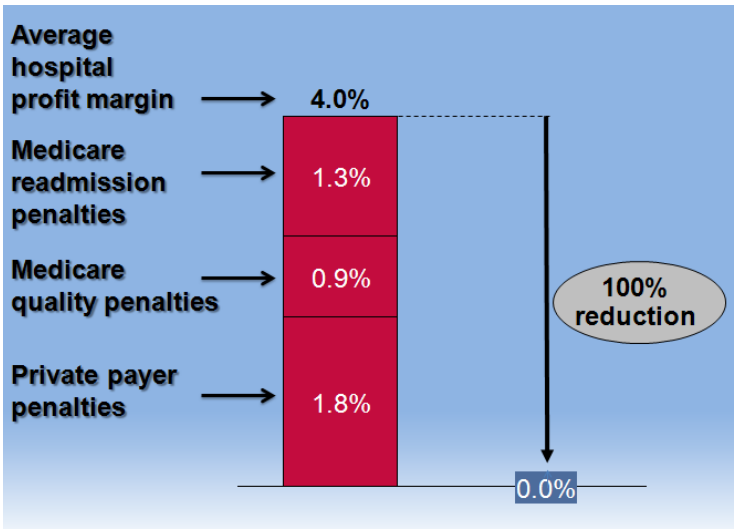
3. Research Plan

3.1. Significance

3.1.1. The importance of hospital readmissions and congestive heart failure

Hospital readmissions represent a major clinical setback for patients and impose considerable financial burden on the health care system. Unfortunately, 1 in 12 patients will be re-admitted within 30 days, at an estimated societal cost of $16.3 billion (Sommers et al. 2011). Recognizing the importance of improving readmission rates, the 2010 Patient Protection and Affordable Care Act includes the Hospital Readmissions Reduction Program, which requires the Centers for Medicare and Medicaid Services (CMS) to reduce payments to hospitals with excess readmissions beginning on October 1, 2012 (Centers for Medicare and Medicaid Services 2013) (Patient Protection and Affordable Care Act 2010). The program focuses on Heart Failure, Acute Myocardial Infarction, and Pneumonia-related readmissions. The penalties are considerable: This year, 2,225 hospitals will face penalties estimated at $227 million. This ranges from 1 to 3% of their total Medicare patients. While this may appear as a small penalty, it represents a major financial burden because hospital profit margins average 4%, thus, as shown in the adjacent figure, these penalties, on top of private payer penalties, can reduce hospital profit margins by 50-100%. Penalties will increase up to 5% in 2015, further eroding profit margins for hospitals that fail to act to reduce readmissions.



CMS has decided to focus on heart failure because it has the highest readmission rate of any diagnosis (24.7%) (Elixhauser et al. 2013). While health care systems have made several attempts to address readmission, cost-effective and meaningful reductions in readmission rates have been "elusive" (Hersh et al. 2013). Readmission reduction programs can be broadly divided into predischarge, postdischarge and bridging interventions. Predischarge interventions include medication reconciliation, patient education, and discharge planning (Hansen et al. 2011). Postdischarge interventions include follow-up telephone calls, postdischarge home visits and patient-activated hotlines (Hansen et al. 2011). Bridging interventions include physician continuity (inpatient/outpatient), patient-centered discharge instruction, and transition coaches (Hansen et al. 2011). However, none of these individual interventions has been shown to substantially reduce the 30-day hospital readmission rate according to one systematic review (Hansen et al. 2011). While several smaller studies have shown a benefit for telemonitoring in heart failure management, the largest study to date of telemonitoring in recently discharged heart failure patients failed to show a significant benefit, with readmission or death (composite primary end-point) in 52.3% and 51.5% of the telemonitoring and usual care patients, respectively (Chaudhry et al. 2010). It is important to note, however, that this study had several limitations, including the use of a relatively simple technology (interactive, telephone based, voice-response system) (Chaudhry et al. 2010).

Taken together, this suggests that there remains significant opportunity to develop more accessible and effective telemedicine solutions to reduce hospital readmission rates from heart failure.

3.1.2. What is the role of sleep apnea in heart failure?

Sleep apnea is a condition characterized by recurrent cessation of breathing during sleep (Gooneratne et al. 2012). Episodes can be either obstructive (in which there is a total cessation of breathing for at least ten seconds), central (in which the physiologic drive to breath is absent), mixed (in which episodes may begin as central but later assume obstructive characteristics) or hypopneas (in which the volume of breathing is reduced, and causes evidence of oxyhemoglobin desaturation or neurologic stress). It is commonly defined by the apnea-hypopnea index, i.e., the number of episodes per hour. Sleep apnea is extremely common in heart failure patients, with prevalences of 51% to 81% (Javaheri et al. 1998) (Herrscher et al. 2011). For this reason, recent heart failure guidelines emphasize the importance of screening and treating sleep apnea (McKelvie et al. 2011). Researchers have also noted an increased risk of death in untreated OSA patients (Javaheri et al. 2011), with one study observing that none of the OSA-treated CHF patients expired during a mean 2.9 year follow-up period (Wang et al. 2007). Treatment of sleep apnea in hospitalized heart failure patients has

demonstrated improvements in systolic function (Khayat et al. 2009). CPAP therapy has also been found to significantly reduce the rate of hospitalization and mortality in heart failure patients (Kasai et al. 2008). In this study, the hazard ratio for hospitalization or death in non-adherent CPAP patients was markedly increased at 4.02; 95% CI, 1.33 to 12.2 (Kasai et al. 2008). Another prospective study noted profound reductions in hospitalization rates for patients with cardiac or pulmonary disorders when treated with PAP (Peker et al. 1997). While most of these studies were in patients with obstructive sleep apnea, the landmark CANPAP study also showed benefits of CPAP on central sleep apnea (Arzt et al. 2007). Treated subjects experienced a greater increase in left ventricular ejection fraction at 3 months and transplant-free survival than controls. Of note, these benefits only occurred in patients whose sleep apnea was effectively treated with CPAP. Furthermore, Khayat and colleagues noted that the presence of central sleep apnea in particular conferred greater risk of readmission than any other risk factor in heart failure patients (Khayat et al. 2012).

Despite this growing body of evidence, sleep apnea is rarely evaluated or treated in heart failure patients: one Medicare database review noted that of 30,719 incident subjects with heart failure, only 545 (2%) received sleep apnea treatment (Javaheri et al. 2011). This highlights that effective diagnosis and treatment of sleep apnea could have a major impact on heart failure management.

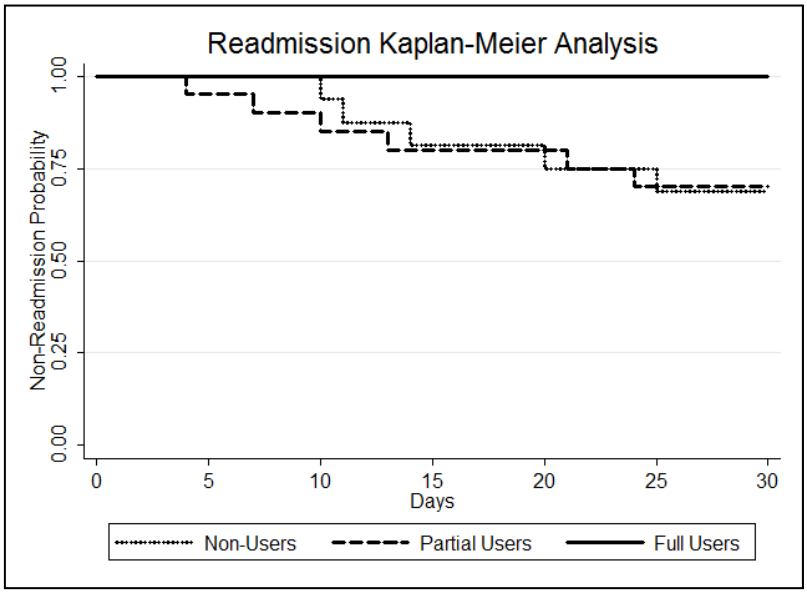
The low rate of sleep apnea treatment in heart failure, the fact that heart failure is the number one cause of readmission, and the growing financial focus on readmissions creates an ideal opportunity to intervene in a focused area, that of sleep-apnea treatment in heart failure. This targeted intervention has the potential to have a high impact on patient care and also be financially sustainable because it would address a very real financial concern faced by health care systems, that of avoiding Medicare penalties for readmission.

3.1.3. What data exists to show that treating sleep apnea can reduce heart failure readmissions?

Isolated case reports have suggested that acute treatment of sleep apnea in hospitalized patients with heart failure can be of significant benefit (Deswarte et al. 2008). This prompted the University of Pennsylvania Sleep Center to establish several years ago a program that allows in-patients on the cardiology service to be evaluated with a polysomnography to diagnose sleep apnea and shortly thereafter receive sleep apnea treatment using an auto-titrating PAP machine, all during their initial hospitalization. The patient can then continue to use the PAP unit at home. These units are linked via wireless modem to allow real-time monitoring of PAP therapy in the hospital and while at home. This prompt diagnosis/treatment program has since been adopted in the past year by other area hospitals and is becoming a model for nationwide care delivery.

We have conducted a preliminary analysis of the first 106 consecutive patients from the in-patient program. These 106 patients were on the Hospital of the University of Pennsylvania Cardiology units for congestive heart failure (87.4%, of which 53.3% had New York Heart Association Class 3 and 41.1% had Class 4 heart failure) or other cardiovascular conditions. Of these 106 patients, 81 (78%) were found to have sleep apnea on their diagnostic in-hospital sleep study; this is consistent with findings from other research that suggest a high prevalence of sleep apnea in heart failure patients (Javaheri et al. 1998) (Herrscher et al. 2011). Of these patients, 80% (65/81) had predominantly obstructive sleep apnea and 20% (16/81) had predominantly central sleep apnea. Patients were then started on PAP therapy the next night while in the hospital and continued on PAP therapy at home.

Readmission and Emergency Department visit rates were then monitored as the primary outcome; this occurred in 16.2% of patients within 30 days after discharge. Patients were divided into PAP full users (adherent >4 hours of use a night), partially PAP users (adherent 0 to 4 hours per night) and non-users. The readmission rates are shown in the related Figure. The most striking finding is that while 29-30% of the partial users and non-users were re-admitted within 30 days, none of the PAP full users were re-admitted (p=0.025). Also of note, only 34% of the discharged heart failure patients were full users of PAP—the majority of discharged patients were either non-users (30%) or partial-users (36%); this highlights the need to develop interventions to improve PAP



adherence. The manuscript related to these findings is accepted for publication in the Journal of Clinical Sleep Medicine pending revisions (peer-reviewed journal).

While these findings are provocative, it is important to highlight the numerous limitations of the above preliminary data. First, this is a naturalistic quasi-experimental study—the patients were not randomized to PAP or sham-PAP. Second, the study has a small sample size. Third, echocardiographic data and other biomarker data was not available to examine physiologic mechanisms. Fourth, follow-up readmission data and PAP adherence data was only available in 56 out of the 81 patients. Despite these limitations, we believe the above data suggests a possible role for sleep apnea treatment for reducing heart failure readmissions.

What could explain this significant reduction in readmission rates? We hypothesize that there are two main avenues of benefit. First, treatment of sleep apnea has been shown to improve cardiac function in heart failure: one randomized trial demonstrated an increase in the left ventricular ejection fraction from 25.0+/-2.8 to 33.8+/-2.4 percent, reduced the left ventricular end-systolic dimension from 54.5+/-1.8 to 51.7+/-1.2 mm and other benefits (reduced heart rate and blood pressure) (Kaneko et al. 2003). Second, it is likely that PAP adherence is also linked to general medication adherence. Research conducted at the University of Pennsylvania has shown that PAP adherence correlates with medication adherence (Platt et al. 2010). However, this has not been noted in all studies (Villar et al. 2009).

Taken together, this suggests three intriguing possibilities. First and foremost: treatment of sleep apnea may be of significant benefit in reducing readmission rates. Second, it is possible that PAP adherence could be a surrogate measure of general medical adherence. Since PAP adherence is being monitored by available usage trackers built into the current PAP devices, this provides a low cost, seamless and wireless means of identifying patients at general increased risk for non-adherence. Thus a patient flagged as being non-adherent with PAP should also be queried for general medication and dietary adherence. Third, there remain significant problems with overall PAP adherence with rates as low as 34%—interventions that could improve adherence, such as the proposed study, could have a meaningful impact.

3.1.4. What is the importance of oxyhemoglobin saturation and why should we measure it?

While the acute stress of an apnea or hypopnea event is important, research suggests that hypoxia may have a greater impact as demonstrated by a stronger association with brain (B-type) natriuretic peptide (BNP), a measure of cardiovascular and hemodynamic stress (Gottlieb et al. 2009). This is of particular importance because, while the current PAP treatment devices have robust internal monitoring capabilities including hours of use, they do not routinely include capturing oxyhemoglobin saturation data.

Recently, new technology has been developed (iHealth oximeter) that can connect via a Bluetooth wireless interface to provide real-time oximetry data. We will propose in Phase 1 to modify the AirCare system to bring in this real-time at-home oximetry data so that we can derive a more accurate and useful measure of PAP effectiveness in treating sleep apnea in heart failure patients. This represents a substantial innovation in care delivery for sleep apnea. Currently, at-home oximetry can be obtained by ordering a nocturnal oximetry through a patient's durable medical equipment provider (DME). However, in actual clinical practice, these are difficult to obtain largely due to inadequate reimbursement by insurance providers. For example, Medicare currently reimburses as little as $13.29 for an overnight oximetry study in the patient's home (Beauliea 2012). Most DME companies lose income on nocturnal oximetry and many refuse to provide this service (Beauliea 2012). At the Penn Sleep Center, we are unable to easily obtain overnight oximety on patients at home using currently available pathways, thus creating significant challenges for patient care.

3.1.5. What are the barriers to treating sleep apnea?

Treatment of sleep apnea can be achieved through positive airway pressure therapy (PAP), oral appliances (these take 2-3 months to custom manufacture), upper airway surgery (removal of the posterior portion of the tongue, tonsils, soft palate, and/or osteotomy cuts in the mandible to advance the mandible along with the tongue), implanted nerve stimulators (in development), weight loss, or oral pressure therapy (oropharyngeal vacuum system) (Gooneratne et al. 2012) (Aurora et al. 2010) (Chan et al. 2007). PAP therapy exists in a variety of forms, such as continuous positive airway pressure (CPAP), auto-titrating positive airway pressure (APAP), bilevel positive airway pressure (bilevel or BiPAP). They all have in common the use of a face mask applied with an air-tight fit to either the nose, or nose/mouth, through which positive airway pressure ranging from 5 to 20 cm H_2O is applied (on average). PAP is the most effective treatment option for sleep apnea and is able to fully treat sleep apnea in over 85% of patients (Gooneratne et al. 2012) (Epstein et al. 2009).

Despite having a highly effective therapy that can be initiated promptly, adherence to PAP is a major limitation as noted in a review conducted recently by our group (Sawyer et al. 2011). There are several reasons why using PAP is so challenging. More significant has been the overall difficult of learning how to effectively apply

the mask to minimize mask leak and maximize patient comfort. Generally, patients are shown how to apply the mask during a 30-45 minute demonstration session during the day when they first receive their PAP machine from a Durable Medical Equipment (DME) provider. Attention to detail and education varies widely, with some DME providers simply dropping the PAP equipment and mask off at the front door, while others make an effort to demonstrate use and train the patient. However, due to significant cut-backs in Medicare reimbursement rates to DME, the level of service they provide has deteriorated over the past year. Fewer and fewer DME companies now make house calls to patients after the initial visit, requiring instead that the patient come to the DME office which may be located far from their home. The DMEs also offer on-call respiratory technician services via telephone, but response times and service quality vary considerably with over 70% of patients in our sleep clinic voicing dissatisfaction with the level of support provided by their DME. Physician offices can also assist patients with their PAP machines and masks, however, most physician visits are 15-20 minutes, thus there is limited time to adequately instruct the patient in how to properly apply the mask. Waiting delays for follow-up sleep physician appointments can average 15-90 days (based on review of Penn Sleep Clinic records).

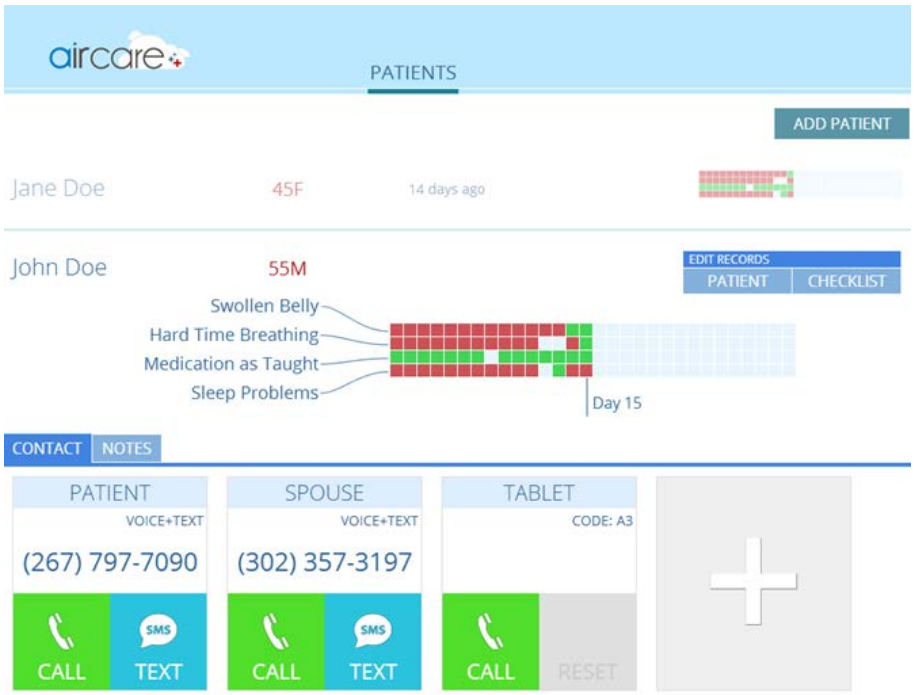
Most strikingly, there is no system in place to provide patients with assistance at night, when they are actually trying to use their machine at home. This glaring omission in care support will be addressed by the current proposal. Indeed, when directly asked what service patients would most appreciate, access to assistance at home at night is ranked as the highest priority based on surveys conducted by our clinic.

3.1.6. How can the AirCare System improve PAP adherence and reduce readmission rates?

The transition to self-care at home after being discharged from an acute care facility is one the most difficult steps in a patient's recovery. Patients are provided with an overwhelming amount of information at discharge, most of which is incomprehensible, difficult to follow, and not fully absorbed. In order to be engaged, patients must have a resource to connect to someone knowledgeable about their disease and their particular priorities and can help them through the vulnerable few weeks right after they are discharged.

AirCare systems offer an inexpensive and easy-to-use solution to prevent unnecessary readmissions though patient checklists, symptom reporting, and mobile video with care providers, such as trained medical assistants, nurses and other care providers. In addition, AirCare risk categorizes patients into high, medium and low risk (red, yellow or green statuses) automatically, which helps us focus resources appropriately. AirCare manages readmissions by offering providers the opportunity to remotely monitor patients as well as virtually connect to patients through phone and secured video chat.

AirCare Tablet: At the touch of a button, care providers are able to connect with patients via laptop, tablet or phone to provide seamless transitions of care, virtual monitoring of compliance, targeted patient education, and individualized care plans. To use AirCare Tablet, patients need an Android tablet with 4G data connection or a computer with a webcam, Google Chrome and high speed internet connection. For patients without home computer access, AirCare has established relationships with mobile providers (AT&T, T-Mobile, etc.) and has negotiated agreements to provide tablets to patients. Providing patients with a preloaded, up-to-date tablet with AirCare Tablet as the primary application maximizes ease of use and simplifies the process of contacting a health care practitioner.



AirCare Voice: AirCare Voice is an automated call system that places calls to patients each morning with 5 customized questions, which the patient can respond to via keypad. This patient data is sent into the same

algorithm as AirCare Tablet, allowing for risk stratification and nurse phone follow-up. This system is more appropriate for patients who prefer phone communication rather than tablet communication.

The system offers several unique benefits for improving sleep apnea adherence as well. First and foremost is access to care providers: the AirCare system can be used to provide patients with at-home assistance in the evening when they are actually using their PAP therapy. Currently, there is no available solution to provide patients with help during this period. Patients can use the AirCare system to contact a sleep technician working the night shift in the sleep lab to receive immediate help if they are having difficulty applying the mask, adjusting the device settings or facing other technical challenges. The video chat feature is particularly helpful in this regard. Second, AirCare is an ideal patient education tool to provide patients access to easy-to-understand video educational content and other instructional material. We propose in Phase 1 to build into the AirCare system educational material related to sleep apnea treatment developed by the Penn site. Third, AirCare Tablet provides health reminders regarding PAP adherence and healthy behavior, including sleep habits, through tablet notifications. AirCare Voice provides these notifications through automated texts and calls. Together, these tools allow AirCare to maximize patient engagement; these will be extended to include sleep apnea. In addition, caretakers are able to become actively involved through AirCare. If permission is granted by the patient, the caregiver can check on PAP usage or daily weight, etc. This caregiver involvement can help the engage the patient's support system in their care, which can also contribute to reducing readmissions.

3.2. Innovation

The current proposal is the first targeted solution that seeks to reduce heart failure readmissions through improved sleep apnea treatment adherence by allowing patients to have ready access to at-home assistance with their PAP throughout the night. Furthermore, we propose to extend these successes in the proposed SBIR by adding several additional features.

Phase 1: We will develop new technology to incorporate real-time at-home pulse oximetry data. This will allow health care providers to have a highly relevant, non-invasive measure of sleep apnea efficacy that extends beyond currently limited options. In addition, we will use structured interviews to identify key areas for educational intervention and develop relevant educational material to embed within the AirCare system for patient access at home. Of particular importance to sleep apnea care, we will use the Phase 1 portion of the study to build in links to an on-call sleep technician. The Penn Sleep Center currently has eight sleep technicians working each night supervising sleep studies. The majority of their active duties occur from 6 PM to 9 PM as they connect patients to the in-lab sleep study equipment. After 9 PM until 6 AM the next morning, they are generally passively observing patients on the monitors or scoring sleep studies from the prior nights. This creates an available, trained sleep technician resource that could assist patients at home using the videoconferencing features of the AirCare Tablet from 9 PM to 6 AM. Since these staff are already working, they can provide assistance to patients affiliated with the sleep clinic without additional financial cost to the sleep clinic. Furthermore, since they are health care employees of the sleep clinic that also takes care of the patient, they are allowed to view patient healthcare data.

Phase II: We will further integrate the AirCare system with the PAP device internal adherence data, creating a directly linked comparison between PAP and a key outcome—nocturnal pulse oximetry. We will develop risk classification algorithms to interpret the real-time oximetry and PAP data and make it available to patients and providers through the AirCare system.

We will then test the AirCare system in a large demonstration randomized controlled trial. This will be the first randomized trial examining the impact of enhanced sleep apnea treatment on 30-day hospital readmission rates.

An additional key innovation is the financial model supporting this intervention. Currently, sleep apnea care is a fee-for-service model that only adequately reimburses physician or nurse practitioner time. Reimbursements for Durable Medical Equipment (DME) companies have declined sharply, with many companies reducing their patient support services in response. Past efforts to develop PAP adherence promoting interventions have not been routinely adopted because they were not reimbursed by payers. The AirCare solution takes a different approach: By demonstrating a financial benefit to hospitals, the AirCare solution can directly approach health care systems to cover the cost of the service. This will allow for a much more rapid uptake of the service than traditional biomedical innovations which require obtaining Medicare approval for new billing codes, a process that can take several years at best and even then may not be adequately reimbursed or approved by other payers. Additional details of this financial model, the first proposed in the sleep apnea field that directly approaches hospital systems, is provided in the Commercialization Plan section.

3.3. Approach

This project represents a partnership between AirCareLabs and the University of Pennsylvania Sleep Disorders Center. AirCareLabs has developed an innovative technology platform that focuses on the 30-day readmission period to create a seamless interface for patient-provider interactions and monitoring of disease metrics. The Penn Sleep Center is an internationally recognized leader in the field of sleep medicine, with over 15 active sleep medicine clinicians and an in-patient sleep consult service that, in preliminary data, has shown that sleep apnea treatment for heart failure patients has the potential to reduce readmission rates. However, the major limitation of the existing in-patient sleep consult service is the low adherence rate (approximately 30%) post-discharge, a limitation that can be effectively addressed using the AirCareLabs solution; this is the core proposition of the current protocol.

The proposed project Phase 1 includes the following key components: 1) Structured interviews with users/care providers; 2) Creating educational content; 3) Developing problem resolution care pathways; 4) Integration of Oximeter data;. The proposed project Phase II includes the following key components: 1) Integration of PAP adherence data; 2) Revising educational content and care pathways; 3) Developing risk classification criteria; and 4) Conducting a large randomized clinical trial to demonstrate effectiveness. These elements are described in more detail below.

We propose to utilize the Fast Track mechanism because the compelling preliminary data suggest the potential for a significant improvement in patient outcomes; all the elements of the program are in place to allow for implementation; and the rapid evolution of the competitive landscape relies upon a first-to-market approach to gather crucial market share to improve commercialization prospects.

3.3.1. Phase 1 Plan

3.3.1.1 Task 1.1: Structured interviews

We will conduct one-on-one interviews with key stakeholders—patients and sleep medicine providers (physicians/nurse practitioners, sleep study technicians). These interviews will be used to maximize usability, resolve potential problems with the user interface, and identify key educational content materials.

The interviews will be conducted by a team consisting of one interviewer (Dr. Gooneratne and/or Mr. Zeng) and a note-taker; this will allow the interviewer to focus on guiding the discussion. Interview participants will be compensated for their time at a rate consistent with their usual hourly salary. The general interview framework is as follows: 1) Open discussion during which the user/provider will be asked to discuss their understanding of heart failure, sleep apnea, and challenges associated with sleep apnea treatment, as well as the current solutions they have attempted to use; 2) A demonstration of the AirCareLabs system, including patient survey feature, assistance request mechanism, and videochat features; 3) Semi-structured interview of their experience with the AirCareLabs system, suggested areas for improvement, and interest in using the system; and 4) They will also be asked to identify areas which they feel would most benefit from educational videos or additional documentation/description, and common problems that merit the development of clinical care pathways.

The general structure above will be applied to the following specific user/provider groups:

Patients: We will conduct interviews with three patient groups at various points along the hospital timeline: 1) inpatients, 2) recently discharged patients and 3) patients at 4-6 months follow-up. We have elected to take this approach because the specific challenges a patient faces at each of these time points may differ, and if we wait until the end of the study to interview the patients, they may no longer recall the problems they faced earlier on, for example, during their hospital admission. We will interview at least 10 patients within each of these three groups. Eligible patients will be those admitted with a heart failure exacerbation diagnosis as their primary diagnosis or active heart failure during their hospital course that requires treatment modification. They must also be newly diagnosed with sleep apnea during their admission. The in-patient group will be approached shortly prior to their anticipated discharge date. The recently discharged patients will be interviewed 1-2 weeks post discharge, and the 4-6 month follow-up group will be contacted at 6 months for interviews.

Sleep Technicians: The Sleep Technicians will be responsible for providing overnight assistance to patients that are having difficulty using their PAP at home. The Penn Sleep Center employs over 30 sleep technicians that staff the 28 sleep study beds at 6 different locations. We will randomly invite them to participate and seek to conduct at least ten interviews using the framework described earlier.

Sleep medicine providers (physicians, nurse practitioners, nurses, medical assistants): The sleep medicine staff that provide day-to-day care for patients will be randomly selected for interviews, with at least 15 interviews, of which a minimum of seven will be with sleep medicine physicians.

3.3.1.2 Task 1.2: Develop educational content

Based on the input provided during the one-on-one interviews, we will identify areas of focus that warrant educational videos and brochures. Sample topics include the etiology of sleep apnea, how PAP therapy works, tips for applying masks, and dealing with mouth/nose dryness. Dr. Gooneratne will produce at least five educational videos of an average duration of ten to fifteen minutes, and ten brochures that can be viewed from the AirCare system. The Penn Sleep Center has a Sleep Education Unit that will assist with the production of the educational content. This educational unit currently conducts live Webinars, has produced educational videos for display in the patient waiting area, and is active in CME events.

3.3.1.3 Task 1.3: Problem resolution care pathways

The sleep medicine providers and sleep technicians will be contacted by patients through the AirCareLabs system for a variety of problems faced by patients as they start using PAP therapy. Based on the input from the one-on-one interviews, Dr. Gooneratne will develop clinical care pathways for resolving the most common problems using evidence-based practices. This will allow for standardized care across different providers. For example, if a patient complains of nasal congestion, one possible set of recommendations would be: 1) three day trial of saline nasal spray; 2) if unsuccessful, five to seven day trial of ipratropium nasal spray; 3) if unsuccessful, review patient nasal spray technique, etc.

3.3.1.4 Task 1.4: Integration of oximeter data

Inclusion of real-time, continuous pulse oximetry data will allow for monitoring a key efficacy measure for PAP: oxyhemoglobin saturation. We will use the iHealth oximeter because of its small size, battery life, low cost, and ability to interface wirelessly via Bluetooth to the AirCareLabs tablet. The unit has an oxyhemoglobin saturation measuring range of 70-99% with an accuracy of ±2% in that range. During Phase I, we will use the available iHealth open API to establish a connection between the AirCareLab system and user data from the oximeter. The system establishes on OAuth client_id and client_secret for each user. The OpenApi can then make requests to the iHealth API Endpoints with the authenticated OAuth credentials. The oximeter itself can store 100 data points, at which time it can send the data, via Bluetooth to the AirCareLab tablet, which will then transmit it via the cellular network to the iHealth server. This data can then be shared with the AirCareLab server using the iHealth OpenApi. The oximeter data can then be queried by users, such as the sleep technician or sleep medicine provider, who wish to monitor the efficacy of the PAP therapy. This powerful technology will allow the sleep medicine team to move beyond simple PAP-derived apnea-hypopnea index values and instead assess the efficacy of treatment on the key endpoint of oxyhemoglobin saturation in a real-time application. We anticipate that the oximeter will be used on a nightly basis for the first week, then as needed if there are continued patient symptoms or any deterioration in the patient's clinical condition.

3.3.1.5 Timeline for Phase 1 Tasks:

Tasks	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Task 1: Structured interviews						
Task 2: Educational Content						
Task 3: Problem resolution scripts and Staff training						
Task 4: Oximetry API connection						

3.3.1.6 Milestones for the Phase 1 project:

1. Structured interviews with users/care providers: Successfully conduct 30 patient interviews, 10 sleep technician interviews, and 15 sleep medicine provider interviews (at least seven with a sleep medicine physician).

2. Educational content: We will create a minimum of five demonstration video clips and ten step-by-step brochures that explain PAP use, mask application, and device care, based on guidance received during the structured interviews.

3. Development of at least ten care pathways to guide sleep technicians and medical assistant staff to assist patients resolve common PAP issues based on focus group work as well as staff training in implementing these scripts.

4. Oximetry data integration using the iHealth API: Successful oximetry data collection will be defined as 1a) maintaining a wireless connection continuously between the AirCare app and the iHealth oximeter for at

least 75% of the study night and 1b) successful transfer of the oximetry data to the central server in 30 minute increments in at least 90% of the cases.

3.3.2. Phase 2 Plan

The goal of Phase 2 is to integrate PAP device data, refine the educational content, develop risk classification content and conduct a randomized controlled trial of the AirCareLab system in a target population of 240 patients.

3.3.2.1 Task 2.1: PAP device data

The PAP devices collect hours of use, estimates apnea-hypopnea index through flow monitoring, and mask leak data on a nightly basis. This data is transmitted wirelessly by modems attached to each unit that connect to the cellular phone network. The large majority of Durable Medical Equipment (DME) providers offer this service since the insurance companies generally require documentation of adherence during the first three months of use to justify continued insurance coverage. This data is stored in a central server maintained by each of the major PAP equipment manufacturers, and is shared with the patient's providers through a web portal data review system. The companies also delivery this data in .csv files on a daily or weekly basis to provider groups, such as the Veterans Affairs administration, large group practices such as the Penn Sleep Center or health systems. The general data format is one row per night of use. During Phase 2, we will integrate this data into the AirCareLabs workflow and make it available to patients and providers directly through the AirCare system. We have elected to perform this in Phase 2 instead of Phase 1 because there are already several commercial platforms that allow for patients and providers to view their PAP-device data, therefore this offers less of a competitive advantage than direct integration of oximetry data, which we have therefore prioritized to Phase 1.

3.3.2.2 Task 2.2: Refine educational content

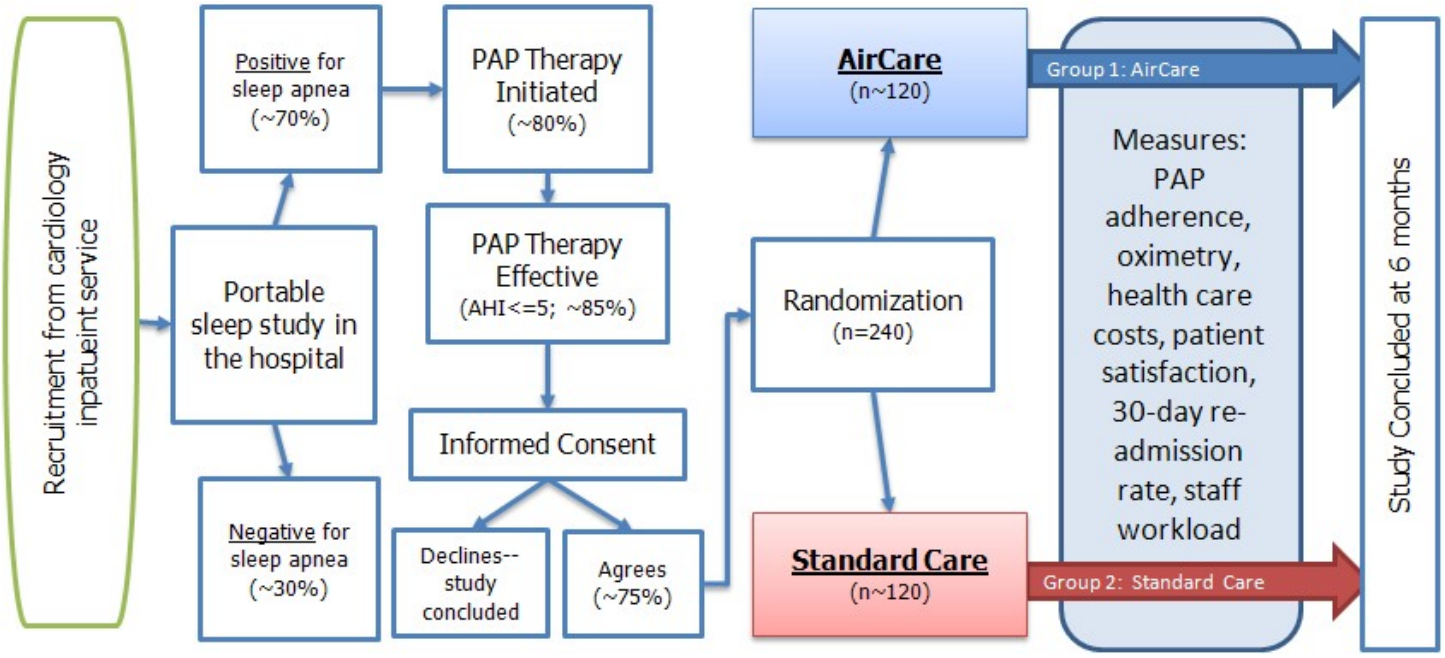
The Educational content created in Phase 1 will be incorporated. Based on the feedback and usage rates of this content, we can then further refine the material. This may include shortening content, adding additional material in a specific section of an existing video/document, or creating new content if necessary. We will be adding a motivational piece, whereby a member of our research staff will contact patients to evaluate their progress and issues while using the PAP unit. Patients will be called on Day 1, 2, 5, 7 and weeks 2, 3, and 4.

3.3.2.3 Task 2.3: Develop risk classification criteria

One of the strengths of the AirCare system is the ability to query the user data on a daily basis to identify patients at high risk for readmission. For example, patients that show low rates of PAP use, increased weight gain, or increased levels of dyspnea, may be at high risk of readmission. The system can generate alerts to health care providers to notify them of this risk so that they can intervene. We will review the symptom data collected during the focus groups to derive preliminary risk classification criteria for non-adherence to PAP therapy for sleep apnea. Candidate targets include low self-report rates of PAP use (such as less than 4 times a week), and persistent oxyhemoglobin desaturations despite PAP therapy (such as persistent desaturations to <90% at night).

3.3.2.4 Task 2.4: Randomized Controlled Trial

The majority of effort during Phase 2 will be devoted to conducting a randomized controlled trial to assess the effectiveness of the AirCareLabs system for reducing 30-day readmission rates in a cohort of heart failure patients with sleep apnea. This study will be conducted at the University of Pennsylvania Health System under the guidance of Dr. Gooneratne (sleep medicine), Schwab (sleep medicine) and Goldberg (cardiology), with assistance from Mr. Zeng and the AirCareLabs team. The proposed study flowchart is shown below.



3.3.2.5 Study Inclusion/Exclusion Criteria:

We have attempted to minimize the study inclusion/exclusion criteria in order to maximize study generalizeability. Individuals must meet the following inclusion criteria prior to study enrollment: 1) Acute heart failure exacerbation requiring hospitalization (primary diagnosis) or admitted for another indication, but whose hospital course has become complicated by heart failure exacerbation. 2) Diagnosis of sleep apnea: Established by an apnea-hypopnea index (AHI) ≥ 5 events/hr consisting of predominantly obstructive apneas and hypopneas on full-night portable in-hospital polysomnography. This is the commonly used clinical criteria for sleep apnea in the setting of underlying cardiac disease (American Academy of Sleep Medicine 2005) (Gooneratne et al. 2012). 3) Age ≥ 18 years (see section on "Inclusion of Children").

Individuals will be excluded from the study for the following reasons: 1) Inadequate sleep apnea treatment with PAP alone: (with up to 2 LPM oxygen) Unable to be adequately treated with PAP to a target AHI<15 events/hr and oxyhemoglobin desaturation nadir >90% and clinical improvement. 2) Unable to perform tests due to inability to communicate verbally, inability to write and read in English; less than a 5th grade reading level; visual, hearing or upper extremity motor deficit (e.g., previous stroke that prevents patient from using PAP treatment).

3.3.2.6 Subject recruitment:

As part of their routine clinical care, patients with active heart failure exacerbation will be evaluated by the sleep in-patient consult service and undergo a portable sleep study. Those with newly diagnosed sleep apnea that elect to start PAP therapy and are adequately treated with PAP therapy will be eligible to participate in the Phase 2 clinical trial. They will undergo an informed consent session using an IRB-approved consent document. Based on our prior experience, we anticipate that approximately 75% will agree to participate. Thus to enroll 240 participants, we must approach 320 heart failure patients with diagnosed sleep apnea. Our preliminary data demonstrated that approximately 80% of admitted heart failure patients have sleep apnea, thus 400 heart failure patients will need to be screened for sleep apnea. The sleep disorders consult service has 10 new consults each week from the cardiology inpatient units for sleep apnea screening, thus approximately 500 new consults per year; we anticipate this volume will be adequate to enroll the required cohort for the Phase 2 study.

We will also recruit subjects from the Presbyterian and Pennsylvania Hospitals, following the same recruitment strategy. We will enroll subjects with a previous OSA diagnosis, who were previously unable to use CPAP. We will also submit a query to the Penn Data store, for de-identified data for the following: age, BMI, gender,

dx of hypertension and CHF, in an effort to expand our recruitment sources. We are also adding an additional recruitment site; Washington University at St. Louis, (WASU), site PI: Dr. Luqi Chi. This site will follow the same recruitment strategy as Presbyterian and Pennsylvania Hospitals.

3.3.2.7 Study Procedures:

After completing the informed consent process, study participants will complete the following study questionnaires (copies are provided in the Appendix): a) Self-Efficacy Measure for Sleep Apnea (Weaver et al. 2003), b) Self-Care of Heart Failure Index (Riegel et al. 2004), c) RAND Medical Outcomes Study Short Form (SF-36) (Ware et al. 1992), d) Epworth Sleepiness Scale (ESS) (Johns 1993). In addition, the medical chart will be abstracted by the study research coordinator to complete the Cumulative Illness Rating Scale (CIRS), gather demographic data, medications and other relevant covariates (Miller et al. 1992). They will then be randomized in a 1:1 ratio to either the AirCareSystems tablet or standard care as described below:

AirCareSystems Group: Study participants in this arm will receive a tablet computer with a pre-installed AirCare application. The tablet will be locked to prevent other usage. All data from previous users will have been wiped from the tablet. The patient will be instructed in the use of the tablet, and will be encouraged to view the installed educational content created in Phase 1.

At the time of discharge, the study participants will leave the hospital with the PAP unit, the tablet computer and an iHealth oximeter. (In the event the patient is discharged before their PSG, they will use the Embletta at-home sleep device to determine eligibility). At home, they will be asked to complete daily, brief questionnaires about their symptoms. They can also use the tablet to submit queries to request assistance with their sleep apnea care. These queries will be answered during the daytime by the day shift sleep technicians or sleep medical assistants according to the standardized care pathways developed earlier. At night, they will be answered by the sleep technicians staffing the 6 active sleep labs (operating seven days a week on all days except national holidays). They will also use the iHealth oximeter on a nightly basis for the first week, then on an as-needed basis thereafter depending upon their symptoms or requests from care providers. It is anticipated that the average study participant will make 2-5 night-time assistance requests, and 3-7 daytime assistance requests. The Risk Classification criteria developed in Task 2.3 will be applied to identify study participants who are at high risk of non-adherence or readmission.

PAP adherence will also be tracked using the built-in device PAP units. Hospital readmissions, ER visits and other doctor visits will also be recorded.

At the end of the first month of treatment, study participants will be asked to return their tablet and iHealth oximeter. They will also be asked to complete the same battery of study survey instruments they completed at the initiation of the study protocol; this will be repeated at six-month follow-up as well.

Standard Care Group: Study participants in the standard care arm will be asked to complete the same survey instruments shortly prior to discharge. They will leave the hospital with their PAP unit. Out-patient support will be provided by the study participant contacting their Durable Medical Equipment (DME) provider for assistance or their sleep medicine provider through the sleep clinic. At the end of the first month, and again at 6 months, they will be asked to complete the same battery of survey instruments they completed at the initiation of the study protocol. PAP adherence, hospital readmissions, ER visits and other doctor visits will also be tracked

3.3.2.8 Data Analysis

Descriptive Comparisons Between Intervention Groups at Baseline: Descriptive analyses will be performed in order to characterize the two study groups (AirCare and Standard Care) and to confirm that the randomization resulted in no clinically significant group differences at baseline in demographic, sleep, and other parameters. If the groups differ with regard to baseline variables and these variables are found to have significant associations with outcomes, secondary analysis of covariance will be used to investigate the degree to which estimated relative efficacy depends on these baseline differences.

Hypothesis: The AirCareLabs system will improve PAP adherence post-discharge relative to standard care. Statistical analysis method: PAP adherence will be defined as at least 4 hours of use per night on at least 70% of the study nights (thus, in a typical 30 day month, the study participant will have used it 21 nights for greater than 4 cumulative hours each night); this is consistent with Medicare PAP usage criteria. We will review the PAP adherence downloads, which provide an objective measure of adherence, to determine what percentage of patients in each study arm (AirCare vs. Standard Care) met the adherence criteria (i.e., a patient may be either adherent or non-adherent with PAP). We will utilize a chi-square frequency comparison for this primary analysis.

3.3.2.9 Sample Size Analysis

The study statistical power will be based on a two-sided Type 1 error rate of 0.05, and a Type 2 error rate of 0.20; these are commonly used criteria for study power calculations.

Hypothesis: We anticipate, based on our preliminary data, that 30% of patients will be fully adherent to PAP therapy (use >4 hours per night for >70% of the month). An improvement in adherence to 50% would represent a clinically meaningful change. Using a power analysis based on the chi-square frequency comparison, we anticipate that a sample size of 93 study participants per group will provide an adequate study power. We will increase this by 30% to factor in study attrition or loss to follow-up, thus a sample size of 120 would be adequate.

3.3.2.10 Timeline for Phase 2 Tasks

Tasks	Month 1-2	Month 3	Month 4	Month 5-17	Month 18-19	Month 20-23	Month 24
Task 1: PAP data integration							
Task 2: Refine Educational Content							
Task 3: Risk Classification Criteria							
Task 4: Study IRB approval							
Task 5a: Randomized Clinical Trial: Enrollment period							
Task 5b: Randomized Clinical Trial: 6-month follow-up period							
Task 6: Data analysis/manuscript generation (30-day readmission analysis)							
Task 7: Data analysis/manuscript generation (6-month follow-up analysis)							

3.3.2.11 Milestones for the Phase 2 project:

1. PAP data integration: Successful oximetry PAP collection will be defined as transfer of the PAP data to the AirCareLabs central server in at least 90% of the study days.
2. Refine educational content: Study participant will be asked to rate their satisfaction with the educational content using visual analogue scales. The educational content will be revised during Task 2.2 in Phase 2. These visual analogue scales will then be repeated during the larger randomized trial (Task 2.4 in Phase 2). Successful completion of this task will be defined as a 20% improvement in study participant satisfaction scores after revising the educational content
3. Risk Classification Criteria: A minimum of ten risk classification criteria will be developed based on review of the data. In our preliminary study, we noted that approximately 70% of study participants were non-adherent to PAP therapy. Thus, successful completion of this milestone will also include the requirement that the ten risk classification criteria flag at least 60-70% of patients as being at risk for non-adherence with PAP therapy.
4. Randomized controlled trial: Successful completion of a randomized controlled trial of 240 study participants, with over 90% study questionnaire data completion.

3.3.3. Known limitations

The experience gathered by the study team implementing the AirCareLab system, as well as the Penn Sleep Center through their sleep consult service, has allowed us to address many of the potential barriers to implementing this proposal. Specific issues that warrant consideration include the following:

Is a typical heart failure inpatient admission long enough to allow for sleep apnea diagnosis and treatment initiation? Our preliminary data showed an average admission duration of 13.0 (+/-8.7) days—we noted that this was ample time to allow initiation of PAP therapy.

Will other hospitals initiate this program? The area of acute sleep apnea treatment in hospitalized patients is a “hot topic” in the field right now. For example, the American Society of Anesthesiologists has developed a sleep apnea screening tool for pre-operative evaluation, thus highlighting the growing interest in identifying sleep apnea in hospitalized patients. Several studies have linked sleep apnea to adverse outcomes in hospitalized patients and health systems have been sued for failure to diagnose sleep apnea in hospitalized patients. We anticipate that by the time this SBIR proposal is finished, the majority of hospitals will offer some

form of rapid sleep apnea diagnosis service. Several hospitals in the Philadelphia area alone, for example, have initiated an in-patient sleep consult program in the past year. However, all of these programs face the same hurdles faced by the Penn Sleep Center: low PAP adherence rates post discharge. Improving post-discharge PAP adherence rates is thus the target goal of the current SBIR proposal.

3.4. Summary

Hospital readmissions, in many cases, represent a failure of the health care system. Patients, prior to discharge, have had their cardiac status optimized and are in a controlled environment where the hospital staff can help to educate and prepare the patient for a successful discharge. Yet despite this, heart failure patients have the highest readmission rate of any diagnosis. A growing body of data suggests that untreated sleep apnea is a major culprit in this process, with one study showing that the presence of sleep apnea was the largest predictor of readmission risk for heart failure patients (Khayat et al. 2012). Our own preliminary data has shown that only 30% of heart failure patients were adherent with their sleep apnea treatment after diagnosis, and that non-adherence was associated with increased risk of hospitalization. We believe addressing this problem represents a tremendous opportunity to meaningfully improve patient care. Furthermore, the recent introduction of Medicare penalties for readmission, especially heart failure readmissions, creates a financial incentive for health care systems to purchase a solution that reduces readmissions. We believe that the AirCare system offers an excellent product-market fit to address this challenge. AirCare will allow sleep apnea patients, for the first time, to receive assistance at night when confronted with the myriad of potential challenges that face a PAP user. The proposed SBIR will extend the AirCare platform to 1) include wireless oximetry, a key outcome measure for effective sleep apnea treatment; 2) add educational content tailored to sleep apnea and heart failure; 3) create risk classification algorithms that will enhance provider efficiency by flagging at-risk patients; 4) integrate with PAP device data to create a seamless interface for reviewing symptoms, oximetry and PAP adherence for providers; and 5) conduct a large randomized trial to demonstrate effectiveness, a crucial element for a successful commercialization.

The likelihood of the overall project success is high given the successful track record of AirCare in terms of obtaining health system and financial capital endorsement, and the Penn Sleep Center's history of advancement in clinical sleep research. If the project achieves its aims, we have the opportunity to make a meaningful and substantial reduction in hospital readmissions that will both improve the quality of life of the more than one million heart failure patients that are admitted each year and reduce health care costs.