CLINICAL STUDY PROTOCOL NCT03745898

LOFT-HF Study

The Impact of **Lo**w **F**low Nocturnal Oxygen **T**herapy on Hospital Admissions and Mortality in Patients with

Heart **F**ailure and Central Sleep Apnea (LOFT-HF)

Clinical Coordinating Center: The Ohio State University College of Medicine

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Abbreviations and Definitions

AASM	American Academy of Sleep Medicine
ACC/AHA	American College of Cardiology/American Heart Association
AE	Adverse Event
AHI	Apnea/Hypopnea-Index
ASV	Adaptive Servo Ventilation
ATS	American Thoracic Society
CCC	Clinical Coordinating Center
CEC	Clinical Events Committee
CPAP	Continuous Positive Airway Pressure
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CSA	Central Sleep Apnea
CSR	Cheyne-Stokes Respiration
CTMO	Clinical Trials Management Office
CV	Cardiovascular
CVA	Cerebrovascular Accident
DCC	Data Coordinating Center
DMS	Data Management System
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EQ-5D	EuroQol 5D
ERF	Event Review Form
FEV 1	Forced Expiratory Volume within one second
GCP	Good Clinical Practice
HF	Heart Failure
ICD	Implantable Cardioverter Defibrillator
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire

kg	Kilogram
LVEF	Left Ventricular Ejection Fraction
L	Liters
MI	Myocardial Infarction
MICE	Multiple Imputation through Chained Equations
MLWHQ	Minnesota Living with Heart Failure Questionnaire
MOP	Manual of Procedures
NOXT	Nocturnal Oxygen Therapy
NYHA	New York Heart Association
ODI	Oxygen Desaturation Index
OSA	Obstructive Sleep Apnea
OSU	Ohio State University
P&P	Policies and Procedures
PAP	Positive Airway Pressure
PHQ-8	Patient Health Questionnaire-8
PCI	Percutaneous coronary intervention
PM	Project Manager
PROMIS	Patient-Reported Outcomes Measurement Information System
PSG	Polysomnography
QoL	Quality of Life
RROS	Recruitment, Retention, and Operations Subcommittee
SAE	Serious Adverse Event
SAC	Scientific Advisory Committee
SDB	Sleep-Disordered Breathing
SOP	Standard Operating Procedure
SRC	Sleep Reading Center
TBD	To Be Determined
Tsat90%	Percent Time at oxygen saturation < 90%

1. Protocol Summary/Synopsis

Title	The Impact of **Lo**w **F**low Nocturnal Oxygen **T**herapy on Hospital Admissions and Mortality in Patients with **H**eart **F**ailure and Central Sleep Apnea (LOFT-HF)
Objective	The purpose of this trial is to evaluate the long-term effects of Nocturnal Oxygen Therapy (NOXT) on the mortality and morbidity of patients with stable heart failure and a reduced ejection fraction (HFrEF), already receiving optimal guideline-directed medical therapy (GDMT), who have central sleep apnea (CSA).
Study Design	LOFT-HF is a Phase 3, multi-center, randomized, double-blind, sham-controlled outcomes trial with parallel group design, with patients randomized to either control (optimal GDMT plus sham NOXT) or active treatment (optimal GDMT plus NOXT) in a 1:1 ratio.
Intervention to be Tested	Supplemental oxygen delivered via nasal cannula.
Number of Sites	Approximately 30 to 50 centers in the United States (U.S.) and Canada
Number of Patients	858 patients will be randomized to one of the two study groups.
Patient Selection Criteria	Inclusion criteria: • Age ≥ 21 years • History of chronic, stable HFrEF with a left ventricular ejection fraction (LVEF) ≤ 50%, determined by echocardiography, radionuclide angiography, left ventriculography, or cardiac magnetic resonance imaging, within the year prior to enrollment • Central sleep apnea, defined using as an apnea-hypopnea index (AHI) > 15/h with ≥ 50% central events (apnea and hypopneas) • New York Heart Association (NYHA) Class III or IV, or NYHA Class II with any of the following: a. ≥ 1 hospitalization for HF in the last 24 months b. a BMI corrected BNP ≥ 300 pg/ml or a corrected NT-proBNP ≥ 1500 pg/ml c. an ED visit for HF exacerbation where the patient has received an IV diuretic within 12 months of enrollment • Treatment with stable, optimized GDMT according to applicable guidelines in the U.S. and Canada, where stable is defined as the addition of no new class of disease-modifying drug for ≥ 30 days prior to randomization (reasons for intolerance to GDMT must be documented) • In the investigator's opinion, willing and able to comply with all study requirements

	• Able to fully understand study information and sign an IRB-approved informed consent (including HIPAA authorization in the U.S.) Exclusion Criteria • Current positive airway pressure (PAP) use or diagnosis of obstructive sleep apnea (OSA) • Oxygen saturation < 90% at rest during the day • Chronic daytime or nighttime use of supplemental oxygen • Nocturnal oxygen saturation <88% for > 5 minutes unaccompanied by apneas or hypopneas • Participants and their bed-partners who currently smoke in the bedroom • Severe pulmonary disease requiring continuous home oxygen therapy or the continuous or frequent intermittent use of oral steroids or documented severe COPD with FEV1 < 50% • Cardiac surgery, percutaneous coronary intervention, myocardial infarction or unstable angina within the previous 3 months • Cardiac resynchronization therapy implantation scheduled or performed within 3 months prior to randomization • Transient ischemic attack or stroke within the previous 3 months • Primary hemodynamically-significant uncorrected valvular heart disease (obstructive or regurgitant) or any valvular disease expected to require surgery during the trial • Acute myocarditis/pericarditis or other cause of potentially reversible cardiomyopathy (e.g., post-partum cardiomyopathy, tachycardia-induced cardiomyopathy), within the previous 6 months • End-stage (Stage D) HF requiring continuous outpatient intravenous (IV) inotropic therapy, placement of ventricular assist device, listing for cardiac transplantation, or end-of-life care (e.g. hospice care) • Pregnancy or of child bearing potential without a negative pregnancy test within 10 days prior to enrollment • Life expectancy < 1 year for diseases unrelated to chronic HF • Enrolled or planning to enroll in another study that may conflict with protocol requirements or confound subject results in this trial

Primary Endpoint	First occurrence (time-to-first event analysis) of either mortality due to any cause, a life-saving cardiovascular (CV) intervention, or unplanned hospitalization for worsening HF measured over the duration of the trial. Life-saving CV interventions will be identified using criteria that are considered as being equivalent to HF-related death (i.e., progressive pump dysfunction or sudden [arrhythmic] cardiac death), including cardiac transplantation, long-term ventricular assist device implantation, resuscitation of sudden cardiac arrest, or shock from an implantable cardioverter-defibrillator (ICD) associated with sudden loss of consciousness associated with ventricular tachycardia or ventricular fibrillation. Unplanned hospitalizations for HF will be identified when a patient is admitted to a hospital inpatient bed, observation unit, or emergency department for worsening signs and/or symptoms of HF requiring treatment with IV diuretics and/or IV vasoactive medications for HF. Worsening of HF will require evidence of two or more of the following: pulmonary edema; elevated jugular venous pressure; worsening dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, or fatigue; decreasing exercise tolerance; worsening renal function; radiological signs of congestive HF; or elevated BNP or NTproBNP level. A Clinical Endpoints Committee (CEC) will be responsible for finalizing event definitions in a CEC Manual of Operations and adjudicating each of these primary endpoint events, blinded to study assignment.
Secondary Endpoints	<u>Morbidity and Mortality</u> • All-cause mortality, CV interventions, or hospitalization for worsening HF (recurrent event analyses) • CV death, life-saving CV interventions, or hospitalization for worsening HF (time-to-first event and recurrent event analysis) • All-cause mortality or life-saving CV interventions (time-to-first event analysis) • CV mortality or life-saving CV interventions (time-to-first event analysis) • All-cause mortality (time-to-event analysis) • CV Mortality (time-to-event analysis) • Rate of hospitalization for worsening HF (recurrent event analysis)

	Quality of Life and Symptoms • Change in HF disease-specific quality of life, assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) • Change in generic-quality of life, assessed by the EQ-5D • Change in depressive symptoms assessed by the PHQ-8 • Change in sleep symptoms and sleep related daytime impairment (including fatigue), assessed by the PROMIS Sleep Disturbance and Sleep Related Impairment Questionnaires Functional Status • Change in NYHA Functional Class Ranking Secondary morbidity and mortality endpoints will be measured over the full duration of study follow up. Quality of life, symptoms, and functional status endpoints will be measured at baseline and at 6 and 12 months follow up.
Safety Assessments	Continuous assessment of study-related adverse events (AEs) will be collected.
Scheduled follow up	Patients will be followed up on average for a period of about 2.5 years. All patients will be followed, until the last patient randomized completes 6 months of follow up. Thus, minimum follow up time will be 6 months, and maximum follow up is anticipated to be about 4.5 years, assuming that the enrolment accrual pattern is uniform across and completed over 3.5 years. In-clinic or remote study visits will occur at Screening/Consent, Baseline, 6 months, and 12 months. Telephone follow-up will occur at 1 month, 3 months, 9 months, 18 months, and then every 6 months after that, until the last participant completes the study. There will be a telephone assessment for each patient at the end of the study, for final ascertainment of mortal and morbid events. Prior the De-briefing Visit, a follow-up in home sleep study will be performed. At the De-briefing Visit the coordinator will review the baseline and follow-up sleep study results, reveal the participant's treatment arm and provide letters for continuity of care.
Independent Committees	An independent CEC will adjudicate all outcomes associated with the primary and secondary mortality and morbidity endpoints. An Independent Data and Safety Monitoring Board (DSMB) will monitor all efficacy and safety outcomes (including study-related AEs), but will be able to recommend early termination of the trial only for significant excess mortality in the treatment group or for overwhelming evidence of patient benefit or harm.

Statistical Considerations/Sample Size	We hypothesize a treatment effect resulting in a 20% annual reduction in the primary endpoint (all-cause death, life-saving CV interventions, or hospitalization for worsening HF). This treatment effect is comparable to established therapies for the treatment of HF, such as renin-angiotensin system inhibitors, beta-blockers, and mineralocorticoid receptor antagonists. A total sample of 858 subjects (429 in each arm) achieves 90% power at a 5% significance level to detect a hazard ratio (HR) of 0.755, when the annual event rate in the control group is 40%, using a two-sided logrank test.

2. Introduction

2.1. Background information

As reported in the 2017 American Heart Association (AHA) Statistical Update (1), an estimated 6.5 million American adults have heart failure (HF). Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in greater than 8 million Americans with HF (2). Heart failure is associated with substantial morbidity, mortality, and economic costs. One in 8 U.S. deaths have HF mentioned on the death certificate (3). In 2014, HF "any-mention" mortality was 308,976 (3). Hospitalization for HF represents a major public health concern. Hospital discharges for HF in the U.S. have remained unchanged for more than a decade, numbering more than 1 million annually (1), and HF is the number one cause of hospital readmission in Medicare beneficiaries (4). In 2012, the total cost of HF in the U.S. was estimated at $30.7 billion, with 68% attributable to direct medical costs (2). One projection places the total cost of HF in the U.S. at nearly $70 billion, by 2030 (2). Worldwide, these figures may be multiplied 4-fold given the global prevalence of HF of 26 million (5).

Beyond the high rates of morbidity and mortality and the staggering economic cost, HF produces substantial patient disability, impairing quality of life, functional status, and exercise capacity, despite currently available guideline-directed medical therapies (GDMT). For example, advanced HF patients (those categorized in New York Heart Association [NYHA] Class III or IV) comprise about 30% to 40% of the HF population and cannot perform many or any activities of daily living. Thus, beyond GDMT, additional interventions that improve quality of life and exercise capacity and reduce hospital admissions and mortality in HF are needed. One target for intervention that, if successfully treated, has the potential to improve both patient-centered and clinical outcomes is co-morbid sleep disordered breathing (SDB).

Sleep disordered breathing is very common in HF patients, particularly in those with HF and a reduced (left ventricular) ejection fraction (HFrEF), with a reported prevalence rate of 50% to 75% (6-12). Two types of abnormal breathing predominate; obstructive sleep apnea (OSA) and central sleep apnea (CSA) including Cheyne-Stokes Respiration (CSR). Obstructive sleep apnea is seen in 20% to 45% of chronic HFrEF patients (6-12), a rate that is considerably higher than the general population (13), while CSA is also common and reported in 25% to 40% of chronic HFrEF patients (6-12). Importantly, SDB has been associated with high rates of morbidity and mortality in HFrEF patients. In such patients, multiple studies have shown that SDB is a strong and independent risk factor for excess and recurrent HF hospitalizations and for excess mortality (14-19).

There are several mechanisms by which SDB may be detrimental in the setting of HFrEF. These include tissue hypoxia and repetitive arousals from sleep with increased sympathetic nervous system activity (20,21). In patients with OSA, apneas and hypopneas can be directly treated with continuous positive airway pressure (CPAP), which operates as a pneumatic stent to stabilize the collapsible upper airway characteristic of this disorder. While CPAP is a well-accepted treatment for patients with OSA, there is no consensus on how to treat CSA, especially in the setting of HFrEF where instability of the respiratory control system is the major pathophysiological mechanism. Several approaches to the treatment of CSA in HF, including CPAP and other positive airway pressure (PAP) therapies, have been evaluated; none have been yet proven to be safe and effective while some have proven to be potentially harmful.

The largest trial of CPAP in heart failure patients, the Canadian Positive Airway Pressure (CANPAP) study, was terminated early after 200 patients were followed for at least 6 months

(22). After a pre-specified interim analysis, the Data and Safety Monitoring Board (DSMB) recommended the termination of the study because of an early divergence of cardiac transplantation-free survival (the primary endpoint) favoring the control group. Despite this early trend, the overall study outcome was neutral in demonstrating no statistically significant improvement or worsening of cardiac transplantation-free mortality. The authors and others (23) concluded that their data did not support the use of CPAP to extend life in patients who have CSA and HF; however, the door was left open to the study of other PAP therapies in this setting.

Following CANPAP, it was hypothesized that a more efficient PAP way of treating CSA, namely adaptive servo ventilation (ASV), might prove useful in the treatment of HFrEF patients (24). Adaptive servo ventilation automatically adjusts pressure support to stabilize and reduce the ventilation of patients with CSA and has been shown to significantly lower the apnea hypopnea index (AHI), in such patients (25,26). However, a large randomized controlled outcomes study of ASV in HFrEF patients with CSA not only failed to meet its primary endpoint of reducing the combined outcome of death from any cause, life-saving cardiovascular (CV) intervention, or unplanned hospitalization for worsening HF due to futility, it also demonstrated significant increases in all-cause and CV mortality, by 28% and 34%, respectively (27). The results of this study, the Treatment of Sleep-Disordered Breathing with Predominant Central Sleep Apnea by Adaptive Servo Ventilation in Patients with Heart Failure trial (SERVE-HF), have resulted in a contraindication for the use of ASV for the treatment of CSA in HFrEF patients, following an urgent safety warning released in May 2015 (28). The SERVE-HF investigators hypothesized one of the reasons accounting for the treatment-associated increase in mortality was the increased intrathoracic pressure associated with the PAP therapy adversely affecting cardiac physiology (27,29). Although a second large trial evaluating ASV in heart failure (Effect of Adaptive Servo Ventilation on Survival and Hospital Admissions in Heart Failure [ADVENT-HF]; www.clinicaltrials.gov; NCT01128816) is underway, that study is enrolling patients with both OSA and CSA and is not powered to specifically address the role of treatment of CSA in HFrEF.

Thus, the outcome of SERVE-HF left few options and none proven for the treatment of patients suffering from CSA and HFrEF, highlighting the need to rigorously test alternative treatments. This study protocol is a response to the imperative to identify and rigorously evaluate alternative treatments for patients with HFrEF and CSA, a group with particularly high morbidity and mortality. One such treatment is low flow nocturnal oxygen therapy (NOXT), which provides a physiologically sound approach for blunting hypoxemia-associated physiological stresses and sympathetic activation, as well as a means for stabilizing the ventilatory control abnormalities characteristic of CSA, that is postulated to improve patient-centered and clinical outcomes in HFrEF. To date, no adequately powered randomized controlled outcomes trial of NOXT for the treatment of CSA in HFrEF has been performed.

2.2. **Study Rationale**

In the current study, the role of nocturnal oxygen as a physiologically-sound option for treating patients with CSA and HFrEF will be evaluated. The pathogenesis of CSA (and CSR) in HFrEF relates to an increased gain of the respiratory control system to hypoxia and sensitivity to hypocapnia, which together trigger recurrent cycles of hyperventilation and central apneas (21,30). Hypoxia amplifies the controller gain for changes in $PaCO_2$ and reduces intrapulmonary gas stores of oxygen (causing “under-damping”). Accordingly, use of low flow oxygen can stabilize the breathing pattern by reducing the hyperventilation phase of CSA and the subsequent hypocapnia that leads to apneas. Oxygen supplementation also attenuates the individual’s overall exposure to hypoxia, a known contributor to sympathetic over-activity,

ischemia, pulmonary hypertension, and vascular dysfunction (21,30). The adverse effect of hypoxemia was highlighted in the results of a recent large observational study in patients with HFrEF that reported that overnight hypoxemia predicted mortality more strongly than AHI (31). Specifically, this study demonstrated that it was the time below a saturation of 90%, and not the AHI, that predicted excess mortality in a dose dependent manner. This association between nocturnal hypoxemia as a more potent predictor of mortality than the AHI in HFrEF patients has been observed by others.

The impact of supplemental oxygen on clinical and physiological outcomes in patients with HFrEF and CSA was recently summarized in a systematic review (32). Several small short-term studies in patients with HF have shown that low flow oxygen virtually eliminates overnight hypoxemia and improves the number of central apneas, as well as decreases arousal frequency and sleep fragmentation (33-39). In one of the first systematic studies of NOXT, 36 HFrEF patients with CSA and an AHI of 15 or greater were treated with nasal oxygen during a full night polysomnography (36). Oxygen therapy significantly decreased the percent of total sleep time with an oxygen saturation below 90% from 23 ± 21% to 0.8 ± 2.3%. The AHI was decreased by nearly 50% (from a baseline average of 49 to 28 on therapy). Two AHI response groups were identified, those with a major reduction (averaging > 80%) and those with a more modest reduction (averaging < 25%); however, oxygen desaturation was virtually eliminated in both groups. Based on the aforementioned strong association between oxygen desaturation and mortality, NOXT has the potential to improve outcomes in both groups of patients. The potential beneficial effects of nocturnal oxygen in patients with HF are also supported by evidence that oxygen can positively impact important predictors of survival in HF, in particular, sympathetic activity (34,35), peak exercise oxygen consumption (35-38), and left ventricular ejection fraction (35,39). From a patient's perspective, oxygen use in HF also has been shown to improve exercise capacity (35), subjective sleep quality (37), and quality of life (35,39,40).

Despite these promising short-term studies, there have been no long-term studies that have evaluated nocturnal oxygen use in patients with HFrEF and CSA. In fact, the longest prior trial that evaluated nocturnal oxygen in patients with CSA was conducted in Japan and followed participants for a maximum period of only 6 months (39,40). With a sample of only 51 patients, this study was under-powered to detect changes in clinical event rates although demonstrated significant improvements in EF, NYHA functional class, and exercise capacity. Several LOFT-HF investigators completed a study showing that 3 months of oxygen use was safe in patients with cardiovascular disease and OSA, improved overnight hypoxemia (41), and improved measures of physical functioning measured by the SF-36 (42). Long term nocturnal oxygen also has been shown to have favorable effects in patients with severe COPD (43). Thus, low flow nocturnal oxygen is a physiologically sound intervention, has been shown to improve physiological targets, is considered to be minimally burdensome and attractive to patients and clinicians, and appears to be safe. The lack of high level evidence to guide treatment of co-morbid CSA with HFrEF, the considerable morbidity and mortality of this condition, and promising short term efficacy and safety data for use of low flow oxygen, provide compelling reasons to rigorously evaluate the long-term role of NOXT on clinically important outcomes.

3. Study Objectives and Endpoints

3.1. Objectives and Efficacy Endpoints

The primary purpose of this trial is to evaluate the long-term effects of NOXT on the mortality and morbidity of patients with stable HFrEF, already receiving optimal GDMT, who have CSA.

The secondary objectives are to evaluate the effects of NOXT on disease-specific mortality; cardiovascular events; patient-reported outcomes (disease-specific and generic quality of life); and functional status. Finally, subgroup analyses are planned to identify which patients treated with NOXT benefit most, examining potential predictors that include baseline assessment of CSR, severity of left ventricular systolic dysfunction assessed by left ventricular ejection fraction (LVEF), levels of hypoxemia, apnea hypopnea index (AHI), circulatory time, loop gain, arousal threshold, as well as important demographic factors including gender.

3.1.1. **Primary Endpoint**

First occurrence (time-to-first event analysis) of either mortality due to any cause, a life-saving CV intervention, or unplanned hospitalization for worsening HF measured over the duration of the trial.

Life-saving CV interventions will be identified using criteria that are considered as being equivalent to HF-related death (i.e., progressive pump dysfunction or sudden [arrhythmic] cardiac death), including cardiac transplantation, long-term ventricular assist device implantation, resuscitation of sudden cardiac arrest, or shock from an implantable cardioverter-defibrillator (ICD) associated with sudden loss of consciousness associated with ventricular tachycardia or ventricular fibrillation.

Unplanned hospitalizations for HF will be identified when a patient is admitted to a hospital inpatient bed, observation unit, or emergency department for worsening signs and/or symptoms of HF requiring treatment with intravenous (IV) diuretics and/or IV vasoactive medications for HF. Worsening of HF will require evidence of two or more of the following: pulmonary edema; elevated jugular venous pressure; worsening dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, or fatigue; decreasing exercise tolerance; worsening renal function; radiological signs of congestive HF; or elevated BNP or NTproBNP level.

The primary endpoint components will be measured over the full duration of study follow up.

A Clinical Endpoints Committee (CEC) will be responsible for finalizing event definitions in a CEC Manual of Operations and adjudicating each of these primary endpoint events, blinded to study assignment.

3.1.2. **Secondary Endpoints**

<u>Morbidity and Mortality</u>

- All-cause mortality, CV interventions, or hospitalization for worsening HF (recurrent event analyses)
- CV death, life-saving CV interventions, or hospitalization for worsening HF (time-to-first event and recurrent event analysis)
- All-cause mortality or life-saving CV interventions (time-to-first event analysis)
- CV mortality or life-saving CV interventions (time-to-first event analysis)
- All-cause mortality (time-to-event analysis)
- CV Mortality (time-to-event analysis)
- Rate of hospitalization for worsening HF (recurrent event analysis)

Quality of Life and Symptoms

- Change in HF disease-specific quality of life, assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Change in generic-quality of life, assessed by the EQ-5D
- Change in depressive symptoms assessed by the PHQ-8
- Change in sleep symptoms and sleep related daytime impairment (including fatigue), assessed by the PROMIS Sleep Disturbance and Sleep Related Impairment Questionnaires

Functional Status

- Change in NYHA Functional Class Ranking

Secondary morbidity and mortality endpoints will be measured over the full duration of study follow up. Quality of life, symptom, and functional status endpoints will be measured at baseline and at 6 and 12 months follow up.

3.2. Safety Assessments

Continuous assessment of study-related adverse events (AEs) will be collected. An independent Data and Safety Monitoring Board (DSMB) will review events.

4. Study Design

LOFT-HF is a Phase 3, multi-center, randomized, double-blind, sham-controlled outcomes trial with parallel group design, with patients randomized to either control (optimal GDMT plus sham NOXT) or active treatment (optimal GDMT plus NOXT) in a 1:1 ratio.

4.1. Enrollment

Participants will be recruited from outpatient clinics and inpatient clinical settings (see Section 10 for Recruitment Plan). To enrich the study population for morbid and mortal events, we will enroll at least 30% of patients with poor prognostic markers, such as HF hospitalization within the prior year and/or elevated outpatient BNP or NTproBNP level. Those screened from inpatient settings for decompensated HF and without a previous clinical sleep study within the past 12 months can be screened prior to hospital discharge, when in a stable, optimized health, using the research PSG device. Baseline morbidity measurements will be continuously monitored to ensure that the study enrolls a high morbidity group (recruitment strategies will be changed if departures from expectation are observed.)

Patients will be screened for SDB, as detailed in Section 8.2. Screening will be documented in a screening log. Based on the assumptions detailed in the sample size calculation (see Section 11.2 for Sample Size Calculation), including a 35% screen positive rate by sleep study, a total of 2,450 patients will need to be screened with sleep studies to randomize a total of 858 patients (429 per arm) eligible patients.

Written informed consent must be obtained prior to any study related procedure. Before final enrolment, all eligibility criteria must be checked by filling in the inclusion/exclusion criteria case report form (CRF) and entered and verified into a secure study web portal.

4.2. Start-Up Phase

There will be a 3-month start-up phase with a limited number of 10 centers participating to

randomize the first 20 patients. At the end of the start-up phase there will be a feasibility-check performed by the Steering Committee and the study sponsor, the National Heart, Lung, and Blood Institute (NHLBI). The Steering Committee, with input from the NHLBI, will decide on the need for changes of study procedures and the need for amendments of the study protocol, if required.

4.3. Study duration

Following the start-up phase, the total study duration is expected to be 4.5 years. Patients will be followed up on average for a period of about 2.49 years. All patients will be followed, until the last patient randomized completes 6 months of follow up. Thus, minimum follow up time will be 6 months, and maximum follow up is anticipated to be about 4.5 years. With a randomization rate of 0.35 patients per center per month, 838 patients will be randomized over approximately 54 months of enrollment (although this period may be extended based on COVID-19 pandemic-related enrollment delays). Enrollment contingencies are planned, should the actual randomization rate be higher or lower than that assumed (see Section 10.4.3).

5. Selection and withdrawal of patients

5.1. Informed Consent

Signed written informed consent forms, written in accordance with country-specific applicable data privacy acts, the Declaration of Helsinki, and the responsible central IRB, will be obtained from all patients prior to any study-related procedure.

The investigator or responsible staff will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient informed consent form. The patient will be given sufficient time to consider the study's implications before deciding whether to participate.

Completion of the informed consent process can occur in-person and/or through remote encounters. Acceptable remote methods of consent include mailing, emailing, and/or faxing of consent documents and telephone or video contact with potential research subjects. REDCap and other 21CFR Part 11 capable and HIPAA compliant electronic data capture systems can be used for documentation of the informed consent process. Regardless of the method used, the informed consent process needs to ensure that all elements of informed consent are adhered to. The manner in which the informed consent process is completed should be fully documented and stored in study files.

Should there be any amendments to the protocol, such that would directly affect the patient’s participation in the study (e.g. a change in any procedure), the informed consent form will be amended to incorporate this modification and the patient must agree to sign this amended form indicating that they re-consent to participate in the modified study.

A signed copy of the patient’s informed consent form must be maintained in the study files. The patient’s permanent medical records should indicate that the patient has been included in the study.

5.2. Study Population

The intended population for this study is patients with HFrEF and predominant CSA. Eligible subjects meeting inclusion/exclusion criteria will be considered for the study. Patients will be recruited from investigators’ cardiology and sleep practices and from the institution’s broad referral network.

5.2.1. **Number of Patients**

The hypothesized treatment effect is a 20% annual reduction in the primary endpoint (all-cause death, life-saving CV interventions, or hospitalization for worsening HF). This treatment effect is comparable to established therapies for the treatment of HF, such as renin-angiotensin system inhibitors, beta-blockers, and mineralocorticoid receptor antagonists. A total sample of 858 subjects (429 in each arm) achieves 90% power at a 5% significance level to detect a hazard ratio (HR) of 0.755, when the annual event rate in the control group is 40%, using a two-sided logrank test, assuming a 10% lost to follow-up rate and a 5% cross-over rate. (see Section 11.4 for Sample Size Calculation)

5.2.2. **Patient Inclusion Criteria**

- Age ≥ 21 years
- History of chronic, stable HFrEF with a left ventricular ejection fraction (LVEF) ≤ 50%, determined by echocardiography, radionuclide angiography, left ventriculography, or cardiac magnetic resonance imaging, prior to enrollment
- Central sleep apnea, defined using as an apnea-hypopnea index (AHI) > 15/h with ≥ 50% central events (apnea and hypopneas)
- New York Heart Association (NYHA) Class III or IV, or NYHA Class II with any of the following:

  a. at least 1 hospitalization for HF within the 24 months prior to enrollment or

  b. a BMI corrected BNP ≥ 300 pg/ml or a corrected NT-proBNP ≥ 1500 pg/ml or

  c. an ED visit for HF exacerbation where the patient has received an IV diuretic within 12 months of enrollment
- Treatment with stable, optimized GDMT or best tolerated according to applicable guidelines in the U.S. and Canada, where stable is defined as the addition of no new class of disease-modifying drug for ≥ 30 days prior to randomization (reasons for intolerance to GDMT must be documented)
- In the investigator's opinion, willing and able to comply with all study requirements
- Able to fully understand study information and sign an IRB-approved informed consent (including HIPAA authorization in the U.S.)

5.2.3. **Patient Exclusion Criteria**

- Current positive airway pressure use or predominantly obstructive rather than central sleep apnea
- Oxygen saturation < 90% at rest during the day
- Chronic daytime or nighttime use of supplemental oxygen
- Nocturnal oxygen saturation < 88% for > 5 minutes unaccompanied by apneas or hypopneas
- Participants and their bed-partners who currently smoke in the bedroom
- Severe pulmonary disease requiring continuous home oxygen therapy or the continuous or frequent intermittent use of oral steroids or documented severe COPD with FEV1 < 50%

- Cardiac surgery, percutaneous coronary intervention, myocardial infarction or unstable angina within the previous 3 months
- Transient ischemic attack or stroke within the previous 3 months
- Cardiac resynchronization therapy implantation scheduled or performed within 3 months prior to randomization
- Primary hemodynamically-significant uncorrected valvular heart disease (obstructive or regurgitant) or any valvular disease expected to require surgery during the trial
- Acute myocarditis/pericarditis or other cause of potentially reversible cardiomyopathy (e.g., post-partum cardiomyopathy, tachycardia-induced cardiomyopathy), within the previous 6 months
- End-stage (Stage D) HF requiring continuous outpatient intravenous (IV) inotropic therapy, placement of ventricular assist device, listing for cardiac transplantation, or end-of-life care (e.g. hospice care)
- Pregnancy or of child bearing potential without a negative pregnancy test within 10 days prior to enrollment
- Life expectancy < 1 year for diseases unrelated to chronic HF
- Enrolled or planning to enroll in another study that may conflict with protocol requirements or confound subject results in this trial

5.3. Stopping and Discontinuation Criteria

When the study is terminated, the nature of termination will be documented (scheduled end or early discontinuation with justification). Discontinuation of the study will be communicated in writing and will be a decision of the Steering Committee, with input from the NHLBI.

5.3.1. Discontinuation Criteria Related to the Study

Discontinuation of the study may be decided due to efficacy criteria or adverse events in either study group at the discretion of the Steering Committee and the Data and Safety Monitoring Board (DSMB), with input from the NHLBI. The DSMB may recommend early termination of the trial for overwhelming evidence of patient benefit or harm, associated with the intervention. Discontinuation of the study can also be decided if patients cannot be recruited in sufficient numbers within a certain time period (i.e., if enrollment milestones are not substantively met).

5.3.2. Discontinuation Criteria Related to the Patient

The patients will be advised in the informed consent form that they have the right to withdraw from the study at any time without prejudice. In the event that a patient drops out of the study, a study stop form will be completed. In the study stop form, the investigator will record the date and the reason of the individual study termination. The patient will be informed that, in addition to their withdrawal, they can request that none of their data should be analyzed. Otherwise, their data remains in the intention-to-treat group.

Reasonable effort will be made to contact any patient lost to follow up during the course of the study, unless they have withdrawn consent and request that no additional contact be made, in order to complete assessments and retrieve any outstanding data and study supplies.

Once randomized, the patient stays within their group regardless of changes in NOXT treatment, and will be followed to the end of the study. An exception is women who become pregnant during the study, who will be discontinued from the study once pregnancy is identified.

Follow-up will also be stopped (data censured) in patients who reach the endpoints of cardiac transplantation or LVAD implantation. Those patients in whom protocol deviation or violation is noticed will remain in the intention-to-treat group and will be followed according to protocol. If a patient from the control group gets NOXT, they will also remain in the study and will be followed according to protocol.

Patients other than those who experience pregnancy, cardiac transplantation or LVAD implants will be followed according to the study protocol, regardless of whether they experience a primary endpoint. This will allow for recurrent event analyses.

Study therapy may be stopped in several circumstances: a) by participant request; b) if the participant's clinical situation changes and his provider prescribes oxygen therapy indefinitely or other therapy that precludes use of oxygen; or c) the participants become pregnant, undergoes cardiac transplantation or LVAD implant. All attempts will be made to continue outcomes assessments on these patients.

5.4. Randomization

Patients meeting all of the inclusion and none of the exclusion criteria will be randomized to one of two groups, a control group receiving optimal GDMT and sham NOXT and a treatment group receiving optimal GDMT and active NOXT.

Patients will be randomly assigned to one of the two study groups in a 1:1 ratio using a permuted block design, stratified by the presence or absence of high-risk markers (hospitalization for HF in the last 12 months and/or an elevated outpatient BNP or NTproBNP level), within sites. Eligible participants will be randomized via a web-based randomization module, initiated by the research coordinator at the participating clinical center. The data management system will confirm all eligibility criteria, and will deliver a randomization identifier (e.g., A or B). Randomization codes also will be linked to identifiers of each oxygen concentrator, providing the ability to assign a participant a concentrator without unblinding local staff. The randomization distributions and system will be re-assessed on a quarterly basis to ensure that it is working as expected. To minimize problems with connectivity, staff will be asked to confirm Internet connectivity at the beginning of the baseline visit to avoid any problems with entry of the randomization case report form. If problems arise with connectivity during a given baseline visit, site staff will be asked to immediately contact the Data Coordinating Center to resolve these; a manually generated randomization assignment would then be generated based upon the subject stratification factor.

6. Investigational Intervention

6.1. General Approach

All patients (treatment and control) will receive standardized sleep education addressing sleep hygiene recommendations that provide guidance on regular bed and wake times; avoidance of alcohol, caffeine, and excessive fluid and food consumption before bedtime; sleeping in dark, cool, and quiet quarters; use of the bed for sleep and intimacy only; avoidance of excessive napping; and avoidance of TV or light exposure before bedtime.

At the end of the baseline visit, after randomization, arrangements will be made to provide each participant a Philips-Respironics Everflo stationary unit concentrator (active or sham) for in-home use, with optional humidification. This may be through a DME or other local resources. Each unit will contain Bluetooth central monitoring capacity, providing ongoing real-time use

monitoring (indications of flow rates and flow rate changes). The sham model delivers pressurized room air, providing the same sounds and appearances as the active device. Inventories for each device (serial numbers, sham versus active) will be monitored at SRC, and the SRC will instruct the local staff/DME provider as to which specific concentrator (serial number to use).

6.1.1. Nocturnal Oxygen Therapy (Treatment Group)

In the treatment group, supplemental oxygen will be delivered via nasal cannula at a flow rate of 3L/min. If the patient cannot tolerate this flow rate despite efforts to add humidification, the flow may be reduced.

6.1.2. Sham Oxygen (Control Group)

In the control arm, sham oxygen (pressurized room air) will be delivered via nasal cannula at a flow rate of 3L/min. If the patient cannot tolerate this flow rate despite efforts to add humidification, the flow may be reduced.

6.2. Adherence Monitoring and Support

Each oxygen concentrator (sham and active) will be equipped with sensors for monitoring the duration of "on" use and for recording each time an oxygen flow delivery change is made. These data, collected using Bluetooth and cloud-based computer technology, will be monitored by the SRC at weekly intervals for each participant throughout the duration of the study. Sleep Reading Center personnel will be responsible for identifying participants with average oxygen or sham use of < 4 hours/night and relaying this information to the relevant site for follow-up. Clinical site research staff will query participants on hours of use of oxygen (and hours per night of sleep), during each scheduled study call and visit. Clinical site research staff will respond to reports of low adherence by contacting participants by phone to identify possible barriers, concerns, or side-effects that may influence treatment adherence. Following a protocolized telephone-based adherence intervention modeled after ones that have been developed for CPAP (44), they will engage in problem solving, implementing recommend changes such as the addition of humidification (for dryness or nasal discomfort) or changes to address noise. The SRC will centrally train site personnel on techniques of motivational enhancement therapy (MET), a client-centered counseling style designed to increase intrinsic motivation and resolve ambivalence about health behavior change (45,46). Sleep Reading Center personnel recently demonstrated a 1.7 hours/night increase in average adherence to CPAP resulting from a simple MET program (44). With the participant's permission, a behavioral sleep therapist may join selected calls with the participant and site staff to reinforce MET techniques. The participant and coordinator will be asked not to use any identifying language in order to avoid sharing any PHI the behavioral sleep therapist. Site staff will contact the SRC should problems related to side effects or resistance to treatment be identified that cannot be resolved using the study protocol, and to discuss any interruptions in therapy (due to intercurrent illnesses or other issues). Staff will identify if alternative approaches are needed, consulting with study investigators as needed. All interactions related to adherence (and potential adverse events) will be recorded on Clinical Report Forms.

6.3. Required Training

Site staff and/or the DME provider will instruct patients on usage of the device. The SRC is responsible for site staff training and certification.

6.4. Concomitant Therapy

All participants will be recruited from centers with expertise in managing HF and will be managed with optimal GDMT for HF, according to applicable guidelines in the U.S. (47,48) and Canada (49), including subsequent guideline updates, where stable is defined as the addition of no new class of disease-modifying drug for ≥ 30 days prior to randomization. Reasons for intolerance to GDMT will be documented, as will post-randomization changes in GDMT.

7. Assessing and Reporting of Adverse Events

7.1. Adverse Events

Generally, an Adverse Event (AE) is any untoward clinical occurrence in a study patient. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease. Some AEs may meet the definition of Serious Adverse Event (SAE). Adverse events are either expected or unexpected. Adverse events may also be Unanticipated Problems.

7.1.1. Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward occurrence or effect that:

- Results in death
- Is life threatening
- Requires inpatient unplanned hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

More than one of the criteria above can be applicable to one event.

Death

Death is defined as either irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including the brain stem. A determination of death must be made in accordance with accepted medical standards. Thereby the condition leading to death is absolutely circumstantial, whether it occurs as outcome of disease or unnatural causes such as accidents. Efforts will be made to avoid double documentation of death as an outcome of other SAEs and as a dedicated SAE itself.

Life-threatening

The definition of a SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death, if it was more severe.

Hospitalization

Is defined as inpatient care of more than one calendar day (overnight admission). Admission for ambulatory diagnostic procedures, overnight observation visits, or ambulatory visits to an emergency ward are not considered hospitalizations for the purpose of SAE reporting, unless any of the other criteria for serious is met.

7.1.2. Expected Adverse Events

An Expected AE is an AE for which the nature, severity, or degree of incidence is known and identified in the product labeling, published literature, or study protocol or follows the natural

progression of or results from routine treatment of any underlying disease, disorder, or condition of the participant experience the AE. Expected AEs associated with polysomnography, the delivery of NOXT using nasal cannula and an oxygen concentrator, and study participation include: skin irritation (e.g., nose or nares, upper lip, face, area above/behind ears); nasal irritation, inflammation, or dryness; nosebleeds; rhinitis; sinusitis; potential increased incidence of other upper respiratory infection; headache; noise irritation: disrupted sleep; anxiety; falls (tripping over tubing or concentrator); fire hazard; oxygen toxicity. The risk of nosebleeds may be increased in a subset of the study population prescribed an oral anticoagulant or those on antiplatelet (especially dual antiplatelet) therapy. This risk will be mitigated through the provision of humidification to any patient complaining of nasal dryness or discomfort. Excluding patients and/or patients with a bed partner who smokes in bed will mitigate the risk of fire. Patients will also be instructed to avoid the use of (flammable) petroleum-based lotions or creams, like Vaseline, on their face, neck, or upper chest. Patients will be warned about the fall-risk associated with oxygen tubing and the concentrator and instructed on how to avoid tripping, especially when awakening at night to use the bathroom or first thing in the morning, through awareness and through optimal positioning of the concentrator and tubing. Investigators must report ~~any~~ suspected Exemplar Expected AEs above thresholds outlined in the Manual of Procedures (MOP) to the DCC, as soon as possible and within the timeframe specified in the MOP following discovery of the event.

7.1.3. **Unanticipated Problems**

An unanticipated problem includes any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research as defined in the MOP; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2. **Recording and Reporting Adverse Events**

At each evaluation, the investigator or research coordinator will determine whether any adverse events (AEs) have occurred. In this trial, all AEs that occur between enrollment and subject exit will be documented in a timely manner and reported to the Data Coordinating Center (DCC). Investigators must report any serious adverse events (SAEs) that are also Unanticipated Problems (events that are unexpected, related or possibly related to the research, and suggest a greater risk of harm to participants or others. to the DCC as soon as possible but no later than 7 days following discovery of the event. The investigator at the site should follow subjects with AEs until the AE has resolved, the condition has stabilized, or the subject exits the trial, and report such follow-up information to the DCC. AEs will be recorded in detail on an AE electronic Case Report Form (eCRF). A description of the event, its severity, and its relatedness to the study intervention will be documented, as well as the resolution of the event. The investigator at the site will adjudicate AEs and assure patient

safety, the DSMB chairperson will receive real-time reports of all USAEs, and the DSMB will periodically review aggregated AE data.

8. Study Schedule

8.1. Study Entry

A patient meets eligibility criteria of the study if the following characteristics are present and documented: all of the inclusion criteria (see Section 6.2.2.) are met and none of the exclusion criteria (see Section 6.2.3.) are met.

8.2. Follow Up and Procedures during the Study Visits/Calls

In-clinic study or remote visits will occur at Screening/Consent, Baseline, 6 months, and 12 months. Telephone follow-up will occur at 1 month, 3 months, 9 months, and 18 months, and then every 6 months after that, until the last participant completes the study. There will be a telephone assessment for each patient at the end of the study, for final ascertainment of mortal and morbid events. Patients potentially meeting eligibility criteria will be consented for further screening. There are two pathways for determination of CSA eligibility for the LOFT-HF trial: a clinical sleep study, polysomnography or home sleep apnea test within 12 months prior to randomization; or a research polysomnogram obtained at home or prior to hospital discharge, when the participant is considered at a baseline, stable condition. The research PSG device is designed for unattended sleep monitoring and contains high quality sensors for quantifying ventilation and oxygenation, and has the ability to measure EEG using self-applied sensors.

Participants will be instructed on how to apply several simple electrodes at home before bed, and return the devices by courier, mail, or direct pick up or drop off. For studies done in the in-patient setting, sensors will be applied by research personnel.

After the results of the clinically-obtained or research PSG are obtained and centrally scored by the SRC, patients meeting sleep eligibility criteria will be invited to participate in a brief baseline examination (remote or in-person) which will include administration of questionnaires (patient-reported outcomes). At the end of the visit, patients will be randomized (stratified by center and the presence or absence of high-risk markers) to sham oxygen (control group) or to NOXT (treatment group). All participants will receive standardized sleep education. A Philips-Respironics EverFlo stationary concentrator for in-home use will be provided to each participant. Devices will be delivered and installed and patients educated on their use by study staff and/or vendors with established agreements with the study (through a DME company, similar to the INOX trial [https://clinicaltrials.gov; NCT01044628]).

Participants will be contacted by telephone (at 1 month, 3 months, 9 months, and 18 months, and then every 6 months after that, until the last participant completes the study) for adverse event and clinical outcomes surveillance. Adverse events and the primary endpoints will be followed until the last subject has undergone a 6-month exam. At 6 and 12 months, subjects will be asked to complete the patient-reported outcomes questionnaires. At study end, each patient and their physician will be provided a copy of relevant clinical information and be offered facilitated referral to a sleep specialist to determine appropriate management of their sleep disorder. Patient-reported outcomes will be collected via validated questionnaires, including the Kansas City Cardiomyopathy Questionnaire (KCCQ), the EuroQol 5D (EQ-5D), the Patient Health Questionnaire-8 (PHQ-8), and the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment Questionnaires. Site personnel will administer these questionnaires, using standard scripted

instructions to patients.

In general, reasonable effort will be undertaken and documented to obtain complete follow up. All follow up visits and calls should be performed within visit windows detailed in Section 8.3, calculated from the date of randomization.

During each study visit and call, the medication taken by the patient as well as the dosage will be recorded. Also, patients will be asked if they take their medication regularly.

Authorized study personnel will document all data requested carefully in the eCRFs, as soon as possible.

8.3. Follow-up Sleep Study and De-briefing Visit

Before the De-briefing Visit, participants will undergo a repeat in-home sleep assessment to serve two purposes: a) provide critical clinical data for use in transitioning to routine clinic care; and b) to maximize the scientific impact of the LOFT-HF study. Participants will be contacted by phone, mail, and/or in-person (coordinating with regularly scheduled clinic or research visits) and offered the opportunity to undergo a repeat in-home research sleep study. The equipment and procedures are the same as described for the research sleep screening visit other than participants will be asked to use their assigned LOFT-HF study treatment during the study and not use the nasal pressure cannula. (The two cannot easily be used together). Devices and equipment will be distributed and returned in-person, by courier, or mail. Study data will be analysed by the BWH SRC, and reports generated with summary data from the overnight sleep study.

At the time of the De-briefing Visit, held on or after Dec 15 2021, when study follow-up will stop, the coordinator will complete assessments for study intervention (sham/NOXT) adherence; collect any pending research data not previously collected (e.g., missing questionnaires); assess for new AEs that occurred up until the final study follow-up date; determine if any medication changes have occurred since last contact thought Dec 15 2021; determine if any clinical outcomes events have occurred through Dec 15 2021; and complete a general rating of improvement/satisfaction survey. After these data are collected, Participants will be provided with a letter that informs the participant of which arm they were randomized to and the results of the baseline and follow-up sleep studies. Participants will be encouraged to discuss further clinical management with their physicians; if needed, the participant will be provided a list of local sleep specialists to access for further clinical follow-up. The coordinator will arrange for return of the oxygen concentrator for final equipment disposition, and if requested, provide a letter to the PCP for continuity of care.

8.4. Detailed Visit Schedule

<u>Screening/Consent</u>

1. Obtain signed written consent
2. Document patient demographics (Health Questionnaire CRF)
3. Perform medical history (Health Questionnaire CRF) and medication review. Completion of a physical examination is optional. Results of a recently completed physical examination during a clinical encounter may be recorded. The site may perform a physical examination at the discretion of the PI either in-person or via telehealth.

4. Evaluate NYHA classification
5. Document that all of the inclusion criteria (except for the sleep eligibility criteria) and none of the exclusion criteria are met (this defines a potentially eligible study patient)
6. Submit de-identified clinical sleep studies to the SRC or administer in-home PSG (if sleep eligibility criteria are met, this defines an eligible patient)

Baseline Visit (to occur within 2 weeks of final eligibility [sleep eligibility] screening)

1. If interim clinical change, repeat medical history and medication review, and reassess NYHA classification. A physical examination is optional.
2. Administer KCCQ, EQ-5D, PHQ-8, and PROMIS questionnaires
3. Provide standard sleep education
4. Randomize patient (within 48 hours of Baseline Visit)
5. Arrange for immediate delivery of oxygen concentrator, by contracted DME provider or staff, for in-home use

   (Note: measures that were not completed during the screening visit and not required to determine eligibility, may be collected at the Baseline Visit.)

1-Month Follow Up Call (± 1 week)

1. Assess for study intervention (sham/NOXT) adherence (Phone contact CRF)
2. Assess for AEs (Phone contact CRF)
3. Determine if any medication changes have occurred since last contact (Phone contact CRF)
4. Determine if any clinical outcomes events have occurred since last contact (Phone contact CRF)

3-Month Follow Up Call (± 10 days)

1. Assess for study intervention (sham/NOXT) adherence (Phone contact CRF)
2. Assess for AEs (Phone contact CRF)
3. Determine if any medication changes have occurred since last contact (Phone contact CRF)
4. Determine if any clinical outcomes events have occurred since last contact (Phone contact CRF)

6-Month In-Clinic or Remote Follow Up Visit (± 2 weeks)

1. Assess for study intervention (sham/NOXT) adherence (Phone contact CRF)
2. Assess for AEs (Phone contact CRF)
3. Determine if any medication changes have occurred since last contact (Phone contact CRF)
4. Determine if any clinical outcomes events have occurred since last contact (Phone contact CRF)
5. Perform medical history (Health Questionnaire CRF) and medication review. A

physical examination is optional.

6. Evaluate NYHA classification
7. Administer KCCQ, EQ-5D, PHQ-8, and PROMIS questionnaires

9-Month Follow Up Call (± 2 weeks)

1. Assess for study intervention (sham/NOXT) adherence (Phone contact CRF)
2. Assess for AEs (Phone contact CRF)
3. Determine if any medication changes have occurred since last contact (Phone contact CRF)
4. Determine if any clinical outcomes events have occurred since last contact (Phone contact CRF)

12-Month In-Clinic or Remote Follow Up Visit (± 2 weeks)

1. Assess for study intervention (sham/NOXT) adherence (Phone contact CRF)
2. Assess for AEs (Phone contact CRF)
3. Determine if any medication changes have occurred since last contact (Phone contact CRF)
4. Determine if any clinical outcomes events have occurred since last contact (Phone contact CRF)
5. Perform medical history (Health Questionnaire CRF) and medication review. A physical examination is optional.
6. Evaluate NYHA classification
7. Administer KCCQ, EQ-5D, PHQ-8, and PROMIS questionnaires

18-Month and Every 6 Months Thereafter Follow Up Calls (± 4 weeks)

1. Assess for study intervention (sham/NOXT) adherence (Phone contact CRF)
2. Assess for AEs (Phone contact CRF)
3. Determine if any medication changes have occurred since last contact (Phone contact CRF)
4. Determine if any clinical outcomes events have occurred since last contact (Phone contact CRF)

Follow-up Sleep Study (within 8 weeks of De-briefing Visit)

1. Obtain signed written consent
2. Administer in-home PSG

De-briefing Visit: (within 6 weeks of the final randomized participant's 6 month visit)

1. Assess for study intervention (sham/NOXT) adherence (Phone contact CRF)
2. Assess for AEs (Phone contact CRF)
3. Determine if any medication changes have occurred since last contact (Phone contact CRF)
4. Determine if any clinical outcomes events have occurred since last contact (Phone

contact CRF)

5. Administer Satisfaction SurveyReview Feedback Letter
6. Arrange for return of oxygen concentrator and referral for further clinical care

8.5. **Screening Polysomnography**

For participants without qualifying clinical sleep studies and not studied during an in- patient stay, in-home polysomnography will be performed using an approach that has low participant and site burden, high accuracy, and is amenable to high levels of standardization. Participants will be evaluated in their homes using a lightweight (4.6 oz), state-of-the art, PSG data collection system (Nox A1 PSG; Nox Medical, Reykjavik, IC), with all data centrally scored by research technicians blinded to all other data. The monitoring device is fully compliant with American Academy of Sleep Medicine (AASM) standards, with capacity for acquiring high resolution signal quality through 32-bit signal processing and 256 kHz sampling on all channels, providing advanced noise reduction and anti-aliasing. The system uses one AA battery that supplies power for up to 12 hours and has 1 GB of data collection capacity per study. The key respiratory data recommended for identifying apneas and hypopneas will be collected: airflow (via a nasal pressure cannula, DC-coupled for linearization), respiratory effort (high resolution thoracic and abdominal inductance plethysmography bands), and pulse oximetry. Heart rate will be measured by ECG sensors. A simplified self-applied frontal EEG system applied near the hairline will provide information to estimate sleep-wake time and identify arousals. Participant burden will be minimized by the use of the Bluetooth enabled oximeter, eliminating the need for cables connecting the finger to a recorder, and through use of self-adhesive electrode pads that are yoked to a single cable.

The PSG devices will be dispensed at the screening visit by staff who will be trained and certified to configure, dispense, download data, and maintain the device. (If this visit is done remotely, the device will be mailed to the participant, along with an instructional video, with follow-up phone/video-based instructions). An operations manual specific to the LOFT-HF sleep study procedure will document each step and that provide site research staff specific instructions on the sleep study process, including the purpose of each sensor. At the end of the screening visit, participants (and their partners when available) will be provided simple instruction brochures with pictures that show the placement of each sensor and videos via a CD or web app. The brochure will provide information on who to contact should any questions or problems arise after the clinic visit, and will detail how to remove the sensors and return the device to the clinic. Participants undergoing the in-home PSG will be asked to practice using the device at the study clinic visit and will be provided ample time to ask any questions about the home sleep study process. When the devices are returned (by courier, staff pick up, or mail, according to site preference), the sleep data containing a participant and site ID and date but no other identifying data will be transmitted electronically to the SRC. The SRC will provide consistent and accurate scoring of all data, blinded to participant information, for evaluating subject eligibility, identifying urgent alerts (see Human Subjects), and for quantifying quantitative metrics for use for predictive modeling. Within two business days, sites will receive electronic reports indicating eligibility status (based on PSG criteria), urgent referrals, and quality grades for each study. Studies that do not meet minimal criteria for acceptability (> 2 hours of artifact free data during the sleep period on respiratory bands, airflow, and oximetry) will be repeated.

Patients recruited during an in-patient hospitalization may undergo a bedside research polysomnography study prior to discharge, when their providers determine their clinical status is near or at baseline. In that circumstance, after research personnel obtain consent, they will directly attach the research polysomnography sensors using the same protocol as provided to patients for self-application for home studies.

Clinical sleep studies performed within 12 months of enrollment will be transferred electronically to the SRC where they will be scored using approaches as similar as possible to the research studies. Studies will be considered for eligibility are those that include at least 4 hours of overnight monitoring, were collected using AASM approved guidelines, and performed within 12months of the baseline visit and at a time when clinically stable (i.e., not in acute decompensation). The sleep study will need to be exported as an EDF file, removing name, MRN, and other identifying information other than date of study. Studies will be transferred via a secure process to the DCC for scoring to evaluate eligibility.

8.6. **Questionnaires**

Study staff will instruct participants on questionnaire completion using standardized scripts. Questionnaire responses will be directly obtained from participants using electronic tablets configured with a streamlined user interface, with appropriate font sizes for an older (frequently Medicare-aged) population. An integrated web application allows progress in completion to be tracked with a parallel display on a second device, enabling staff to assist with questionnaire completion as needed. Forms require all items to be completed before each is closed. Staff will undergo centralized training in use of the electronic data capture system and submit a test sample of data, as part of certification procedures. Each form will have a “Q by Q” guide (specifying responses to sample questions participants may have for each question/item) for staff to refer to if participants raise questions during form completion, supporting consistency.

- Kansas City Cardiomyopathy Questionnaire: The KCCQ is a validated 23-item instrument that quantifies physical function, symptoms (frequency, severity, and recent change), social function, self-efficacy and knowledge, and quality of life in patients with HF (52). It is considered to be a clinically meaningful outcome relevant for research, patient management, and quality assessment (52). A change of 5 points is considered to be clinically significant.
- EuroQol 5D: The EQ-5D assesses preference-based health-related quality of life. It is comprised of a descriptive profile and a single-index visual analogue scale (VAS) (52). It has excellent psychometric properties in patients with HF and cardiac diseases (53,54). The descriptive profile assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses can be mapped to previously derived utility weights, reflecting society’s ratings of the desirability of a given health state. The VAS records the patient’s personal perspective of their current health status (55,56).
- Patient Health Questionnaire-8: The PHQ-8 provides a psychometrically valid measure of depression, a common concern in patients with sleep apnea and HF. The PHQ-8 is an 8-item depression questionnaire with scores categorized as 0-4 (no/minimal depressive symptoms), 5-9 (mild depressive symptoms), 10-14 (moderate depressive symptoms), 15-19 (moderate-severe depressive symptoms), and 20-26 (severe depressive symptoms) (57). A PHQ score ≥ 10 has been shown to have a specificity of 90%, sensitivity of 54%, and a negative predictive value of 88% for detecting depression (58,59). It has been used in heart failure populations to characterize depression (60,61).

- Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance and Sleep-Related Impairment item banks: These two 8-item questionnaires assess self-perceived sleep quality, sleep depth, and sleep restoration. They are designed using item response theory to gauge the severity of sleep-wake problems on a continuum, applicable across a range of conditions and have high measurement reliability and precision (62).

8.7. Clinical Outcomes

A CEC will be responsible for finalizing event definitions in a CEC Manual of Operations and adjudicating each of the primary endpoint events, blinded to study assignment. Brief definitions of endpoint events follow, to provide guidance to the CEC development of event definitions.

8.7.1. Death

Death is defined as either irreversible cessation of circulatory and respiratory functions, or irreversible cessation of all functions of the entire brain, including the brain stem. A determination of death must be made in accordance with accepted medical standards. The CEC will adjudicate the cause of death. While all-cause mortality is a component of the primary endpoint, important secondary endpoints evaluate cause-specific mortality particularly CV death. Deaths will be considered cardiovascular unless a specific non-cardiovascular cause is identified. Deaths classified as “Unknown” will be considered cardiovascular. Cardiovascular death will include such occurrences as death due to sudden cardiac death, heart failure, myocardial infarction (MI), cerebrovascular accident (CVA), CV procedure death, other cardiac death (e.g., death from valvular heart disease), and other vascular death (e.g., death from pulmonary embolism, aortic dissection, or aortic rupture).

8.7.2. Life-saving Cardiovascular Interventions

Life-saving CV interventions will be identified using criteria that are considered as being equivalent to HF-related death (i.e., progressive pump dysfunction or sudden [arrhythmic] cardiac death), including cardiac transplantation, long-term ventricular assist device implantation, resuscitation of sudden cardiac arrest, or shock from an implantable cardioverter-defibrillator (ICD) associated with sudden loss of consciousness associated with ventricular tachycardia or ventricular fibrillation.

8.7.3. Hospitalization

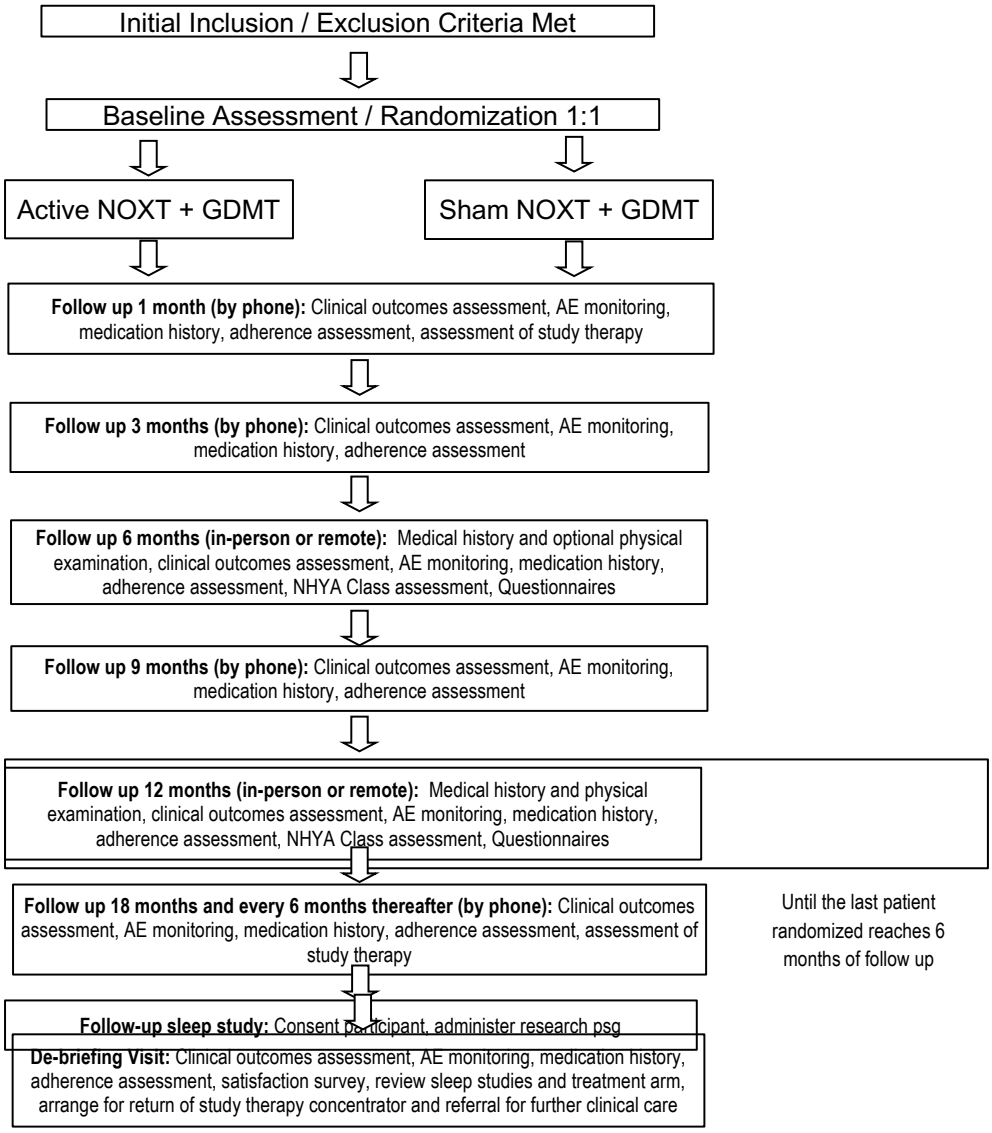
Hospitalization will be defined as a non-elective hospital stay (inpatient, observation, or emergency department [ED] stay) for medical or surgical therapy. Observation and ED stays are included in this definition, given growing financial incentives to hospitals to treat patients in these settings, rather than in the setting of a true Medicare-qualifying inpatient admission. This is especially true in an era of heightened efforts to avoid HF hospitalizations, to avoid Medicare reimbursement penalties. A hospitalization classification will be based on the primary reason for which the subject was admitted, not on the development of new events that occur during the hospitalization or if the subject had additional conditions at the time of admission that were not the primary reason for the admission. The CEC will develop definitions to describe hospitalization for HF, other CV causes (e.g., acute MI, cardiac arrest, CVA, TIA, or pulmonary thromboembolism), and non-cardiovascular causes.

8.8. Overview of Visits

	Screening/ Consent (in clinic****)	Baseline (in clinic****)	1 Month (by phone)	3 Months (by phone)	6 Months (in clinic****)	9 Months (by phone)	12 Months (in clinic****)	18 Monthsthen every6 Months (by phone)	Follow-up Sleep Study	De-briefing Visit (by phone)
Consent patient (*)	✓								✓	
Patient demographics (Health Questionnaire CRF)	✓									
Medical history (Health Questionnaire CRF) and optional physical examination	✓	(**)			✓		✓			
Medication review	✓	(**)	✓	✓	✓	✓	✓	✓		✓
Assess NYHA Class	✓	(**)			✓		✓			
Document inclusion/exclusion criteria	✓									
Administer research PSG	✓ £								✓	
Randomization		✓								
Provide sleep education		✓								
KCCQ, EQ-5D, PHQ-8, PROMIS		✓			✓		✓			
Home study therapy concentrator delivery(***)		✓								
Adherence assessment (Phone contact CRF)			✓	✓	✓	✓	✓	✓		✓
Clinical outcomes assessment (Phone contact CRF)		✓	✓	✓	✓	✓	✓	✓		✓
Adverse events monitoring (Phone contact CRF)		✓	✓	✓	✓	✓	✓	✓		✓
Return of home study therapy concentrator										✓
Satisfaction Survey										✓
Review sleep study reports										✓
Review treatment arm and referral for further care										✓

(*) Patients will be re-consented following any protocol amendments requiring changes in the written informed consent form.
(**) Assessments will be repeated if there has been a change in the patient's clinical status since screening/consent.
(***) Arrange for immediate delivery by contracted home DME provider.
(****) Could occur remotely as needed.
£ For patients without a clinical qualifying sleep study within the prior 12 months

Study Flow Diagram



CSA, central sleep apnea; NOXT, nocturnal oxygen therapy; GDMT, guideline-directed medical therapy; AE, adverse event; NYHA, New York Heart Association

9. Investigative Site Information

9.1. Investigative Site Selection

Sites will be selected for participation based on the following criteria:

- A sleep medicine specialist (investigator) with experience and knowledge of SDB
- A cardiologist/HF specialist (investigator) with experience and knowledge of HF
- A large patient population to identify potential candidates for study participation within the given study timeframe
- Sufficient resources within the site to conduct the screening, enrollment, data collection, and follow-up requirements of all subjects
- Willingness and interest in conducting the study

Sites will have demonstrated interest and accomplishment in the field of SDB in HF and have conducted and/or participated in prior studies in this arena. It is expected that there will be coordination between the sleep medicine specialist and cardiologist/HF specialist. The primary investigator (PI) is responsible for the overall conduct of the study. The PI may train and designate person(s) to conduct study-related activities but must retain overall responsibility for the trial. All training and delegation of tasks will be documented. While a single site PI will be identified for regulatory (IRB) purposes, the LOFT-HF study will consider the lead sleep medicine and the lead cardiologist/HF specialist as Co-PIs, thus promoting close collaboration between the two disciplines. These Co-PIs, along with site Co-Investigators and research coordinators and the LOFT-HF leadership team, will be referred to as the LOFT-HF Study Group.)

9.2. Site Training

Protocol-specific training and education customized to the specific roles of all investigational site personnel will take place during a central training session, during site visits, and throughout the study as needed. All training will be documented and staff will be required to be certified for study specific procedures. All study personnel, including new study personnel added during the course of the study, must be trained and delegated prior to performing any study-related activities.

10. Recruitment and Retention Plan

10.1. Site Selection Process

One of the most important precursors of effective recruitment and retention throughout the duration of the LOFT-HF trial is the selection of key clinical research sites with proven historical records of strong performance in HF and sleep medicine research trials. To address this fundamental base, we have chosen prospective sites using rigorous standards such as requiring evidence of investigator trial experiences; sufficient patient population; and detailed descriptions of research infrastructure including accreditation, number of experienced research personnel, and volume of active trials. Every site chosen by the CCC and DCC has established local infrastructures for the performance of clinical studies and proven track records of accomplishment in HF and SDB clinical trials which has been documented in administered site surveys. Site surveys solicited the following information from each potential LOFT-HF site: contact information; estimate of site specific HF and CSA populations including volume and demographics; current practices for treatment of CSA in patients with HF at each

site; defined referral base; presence of SDB screening in HF program; HF and SDB clinical research trial portfolios including site performance metrics; history and findings of FDA audits; agreement to Central IRB use; and anticipated timeline for execution of clinical trial agreement. In addition, we will require commitment of both a sleep medicine and cardiology physician to serve as Co-Principal Investigators in order to ensure symbiotic collaboration in identification of at-risk patients and subsequent clinical management. Strategic site selection by the CCC and DCC is one of many critical steps in the process of securing target enrollment in a timely fashion.

To complement the process above, we planned on utilizing the Trial Innovation Network (TIN) services to identify strategic collaborators in an effort to identify secondary and tertiary sites. This TIN collaboration takes place during the UG3 phase. Our aim is to identify a minimum of 10 sites that would be activated if suboptimal recruitment rates are observed.

LOFT-HF sites should have expertise in sleep medicine and cardiology in order to ensure symbiotic collaboration in identification of at-risk patients and subsequent clinical management.

In addition, as of August 2019, the CCC established a new partnership with the Heart Failure Society of America (HFSA) Research Network. This partnership is a novel process that will take advantage of an established organization with excellent track records in supporting heart failure trials. The new relationship will be on an ongoing process that will continue throughout the duration of the trial. The arrangement will allow LOFT-HF to access a vast network of vetted research sites to add to or replace non-performing site on ongoing basis. A revised low burden-low cost site activation approach, along with vigilant site monitoring plan, combined with the TIN and HFSA research network partnership will ensure robust enrollment and achievement of accrual targets.

Another aspect to the partnership with TIN is the relation with an assigned Trial Innovation Center (TIC) to develop customized electronic medical record (EMR) feasibility queries to be distributed to the Clinical Translational Science Award (CTSA) consortium.

10.2. **Oversight of Enrollment Progress**

The LOFT-HF Executive committee will diligently oversee study progress through regular meetings and sophisticated project management tools such as the internet-based software application, Slice, that will be used to track enrollment, stratification factors (e.g., proportions with high morbidity risk factors) and screen failure rates in real-time. Committee members will be responsible for analyzing progress reports, interpreting barriers to enrollment, and deploying the appropriate risk mitigation practice (i.e. site-specific additional training, issuing broad guidance's, or protocol amendments). We will use Pareto analysis to capture and analyze incidences of screen failures and protocol deviations as one of many tools to identify trends in protocol compliance so that preemptive actions can be implemented to avert potential endemic complications.

A Recruitment, Retention, and Operations Subcommittee (RROS) will be established which will include Research Coordinators from representative clinical sites, the CCC Project Manager, and two site PIs. The committee will design recruitment brochures, oversee the development of newsletters, and provide input into developing the community-facing web portal. Recruitment and retention statistics will be posted in real-time on a study web site, including graphs that show deviations from projections. Sites, which fail to meet projections for 2 consecutive months, will be asked to provide a report with an analysis and action plan to the Steering Committee. If continued lags are observed, the study PIs (Williams; Redline), in

consultation with the DSMB and NHLBI, will determine further actions, which may include replacement of the site.

10.3. Recruitment and Retention Practices

10.3.1. The 3E Approach

The CCC will work closely with the DCC to development training and certification requirements during the UG3 phase that is aimed at successful recruitment and retention. We plan to use a trident approach to recruitment and retention training that is focused on education, empathy, and engagement, the 3E Approach, coined by the OSU Clinical Trials Management Organization (CTMO). In our experiences in leading multidisciplinary multi-site trials, we believe education is the most powerful tool in the recruitment and retention practices toolbox. Extensive training of research personnel will focus on equipping study coordinators and study nurses with sufficient knowledge of heart failure and sleep disordered breathing. Although we have chosen experienced sites that have performed well in either heart failure or sleep medicine research trials, we understand that each site may be organized in disease-specific groups and as a result, are most well versed in single disease trials. Thus, we will need to thoroughly provide all research personnel with information related to the mechanism of CSA, the consequences of maintaining a hypoxic state and activated sympathetic nervous system in the context of heart failure, the negative relationship between heart failure with untreated SDB and mortality and hospital readmissions, and the importance of a simultaneous treatment approach. We know that if research personnel understand the physiology and scientific basis for the trial, their knowledge may translate into more confidence in describing the objectives of trial to at-risk patients which will increase the likelihood their message is well-received. Proper education of site research personnel is essential for countering misconceptions with evidence-based facts and statistics. The CCC and DCC will be responsible for designing and implementing training; however, we will encourage site Co-PIs to provide supplemental education to their study coordinators and study nurses on a regular basis.

Drawing from the successes of the OSU Sleep Heart Program, training will encompass the importance of empathy in recruiting at-risk patients. Our philosophy has been to “meet people where they are” by acknowledging the fears and concerns of patients with heart failure, making a genuine effort in understanding their challenges, and exhibiting patience as the majority of patients with heart failure are elderly. The training modules will address common rationales of prospective patients that research personnel may have to confront and ways of handling these situations. We will encourage research personnel that may be arranged on disease-specific teams at each site to share experiences with each other and the broader community of research personnel across sites via posting comments on the study website. The generated discussion should result in the proactive suggestions that will translate into better recruitment and retention of participants in the LOFT-HF trial.

Multi-faceted engagement practices will be stressed in all training initiatives for recruitment and retention. Research personnel will be encouraged to form genuine bonds with prospective patients and enrolled patients. The training will address the relationship between rates of retention of enrolled patients with the formation of good relationships between research personnel and patients. In addition to these primary relationships, the training will be applicable to the broader heart failure and sleep medicine clinician community at each site. It is important to realize that the LOFT-HF trial will not occur in a vacuum; other clinicians must be engaged as they will interface with prospective and enrolled patients, delivering care and

may be a potential source of referrals. Therefore, training in-services for various clinical teams including palliative medicine, patient advocacy groups, and social workers, will be provided at the request of each academic site and recruitment materials will be provided to the clinical community as a buy-in measure to generate awareness and support of the LOFT-HF trial. Training and recruitment materials will explicitly address the relevance of the LOFT-HF trial in the context of current international clinical practice post SERVE-HF, thereby presenting a compelling argument in favor of the prioritization of LOFT-HF trial in the setting of other overlapping clinical trials. OSU CTMO routinely puts this comprehensive approach to community engagement into practice during implementation of multi-site research trials.

Each site also will receive nearly real-time feedback on recruitment activities through the study web portal, which displays recruitment graphs by time and site, and includes actual versus projected numbers. This provides positive feedback, allows each site actual data to examine and use for planning and trouble-shooting, and helps to quickly identify sites (and best practices) that can inform study-wide procedures.

10.3.2. **Screening, Approaching, and Consenting**

The LOFT-HF protocol will be inclusive of multifaceted recruitment practices such as in-person recruitment from both HF and sleep clinics and during hospitalization for acute HF, as well as mailed SDB screening questionnaires. Study coordinators and nurses will identify patients by daily screening of hospital admission rosters for patients diagnosed with acute HF and patients scheduled for routine follow-up in outpatient HF clinics. In addition, potential research patients will be identified by the Co-PIs, sleep medicine and cardiology providers, as well as referrals from patient advocacy groups and the broader clinical community including social workers, patient care resource managers, and palliative care specialists. Study coordinators and nurses will confirm eligibility thorough review of the medical record, approval of site investigators, and approval from the CCC as needed. After initial eligibility criteria are confirmed, patients will be asked to undergo an in-home sleep study (PSG) to evaluate SDB if needed. Those screened from inpatient settings after admission for decompensated HF and without a previous clinical sleep study within the past 12 months can be screened prior to hospital discharge, when in a stable optimized health, using the research PSG device. All sites will be provided with screening tip cards including inclusion and exclusion criteria and an eligibility flowchart. Notably, patients under the age of 21 are ineligible for the trial and will not be approached. Women of childbearing potential may be approached and will be eligible for the trial once a negative pregnancy test is confirmed. Once Good Clinical Practice (GCP) and protocol training has been completed and research personnel have received study certifications, those with the delegated authority to consent patients for the LOFT-HF trial, primarily study coordinators and nurses, will be responsible for approaching prospective patients and initiating and completing the informed consent process. The consenting coordinators and nurses will be experienced clinical research professionals as determined prior to site activation. Patients will sign an informed consent to authorize participation in the study prior to undergoing the sleep study screening procedure or submission of a clinically obtained sleep study to the SRC. Patients with confirmed diagnosis of CSA, and otherwise eligible, will be eligible to be randomized. Study personnel will record inclusion and exclusion criteria in an eCRF. Before final enrollment, these criteria will be entered and verified into a secure study web portal.

The primary PI will be responsible for the overall conduct of the study. The PI may train and designate person(s) to conduct study-related activities but must retain overall responsibility for the trial. All training and delegation of tasks will be documented.

10.3.3. Recruitment of High-Risk Subgroup

Participants will be recruited from outpatient clinics and inpatient clinical settings. To study a high-risk group we will prioritize recruitment strategies that target patients based on poor prognostic markers, including hospitalization within the prior year and/or an elevated BNP or NTproBNP level, to meet the goal of recruiting at least 30% of the sample with high-risk markers. Moreover, the requirement for CSA alone identifies a population with high event rates. We will not use a run-in design that would select samples with better prognosis. Based on the assumptions detailed in our power calculation, including a 35% screen positive rate by sleep study, we will need to screen a total of 2,450 patients with sleep studies to randomize a total of 858 patients (429 per arm). We will stratify randomization based on the presence of high-risk markers. We will monitor total event rates by recruitment sources and the presence of high-risk markers and adjust recruitment strategies, if needed, to ensure our actual event rates are comparable to the estimated event rates.

10.4. Recruitment Rates, Timelines, and Milestones

10.4.1. Year 1: Start-Up or UG3 Phase

During the third quarter of Year 1, we will attempt to activate10 clinical sites will be activated. The first enrollments will then occur in the last quarter of Year 1, which is anticipated to be in May 2019. A total of 20 patients will be targeted for randomization during the last quarter of this phase. Before the end of Year 1, an additional 20 sites will be activated to begin enrolment at the beginning of Year 2 (the UH3 Phase), bringing the total number of active sites to 30. Approximately 10 additional sites will be identified to serve as potential replacement sites. During the first quarter of Year 1, we will submit a request for TIN services in site identification and we anticipate to meet our target number of secondary and tertiary sites by fourth quarter of Year 1.

10.4.2. Years 2-5: Completion of Enrolment or the UH3 Phase

Assuming the accrual pattern is constant across time (after a slower ramp up in the first year for site activation) at 0.35 patients per center per month, the following milestones will be reached within 54 months: 25% of target enrollment (n=215) in Jan 2021, 50% of target enrollment (n=429) in Jan 2022 75% of target enrollment (n=644) in Jan 2023, and 100% enrollment (n=858) in January 2024.

10.4.3. Recruitment Rate Contingencies

Based on prior experience and on a survey of proposed investigational sites, the expected rate of randomization is 0.25 patients per center per month. The possible range of assumed randomization rates is 0.25-0.5 patients per center per month (or a screening/consent rate of about 1.5 to 3 patients per center per month). The revised site number is 50 as discussed previously. The decision to open additional sites will be made early based on the monitored monthly accrual target. Given the per patient reimbursement to sites, there is little additional cost to opening new sites. The updated budget and revised site activation process will ensure low cost and burden of adding additional sites. The CCC is committed to cover any cost overruns in site initiation fees (estimated to be $40,000 or less) via its own contingency funds, if an expansion of sites becomes necessary. Alternatively, the period for patient enrollment and randomization could be extended, within the current budget limits. However, this is a less preferable contingency, as completion of enrollment and randomization on schedule is essential to providing a timely assessment of the central hypothesis of LOFT-HF.

10.5. Recruitment and Retention Monitoring

Successful recruitment and retention are critical for the success of any clinical trial and are often more challenging in operation than anticipated during planning. Extensive experience with strategies for optimizing recruitment and retention, including careful selection of participating sites, ongoing monitoring and real-time feedback, capitating payments, providing patient stipends, and sharing expertise across sites in “what works”, will be utilized. Each clinical center has experience in sleep and CV trials and has direct access to large numbers of patients with HF. Sites have Co-Is with good working relationships and expertise in both sleep medicine and cardiology, promoting multi-disciplinary collaboration. A Recruitment, Retention and Operations Subcommittee (RROS) will be established that will include coordinators from representative clinical sites, the CCC Project Manager, and two site PIs.

The committee will design recruitment brochures, oversee the development of newsletters, and provide input into developing the community-facing web portal. Patient representatives from a sleep apnea patient network will provide input into recruitment materials to ensure patient-centeredness. The importance of recruitment of women and minorities will be stressed during training, and we will work with site personnel to use various recruitment materials in ways that that promote recruitment of these populations (i.e. placing materials in women’s health clinics and on community accessible websites affiliated with the site). We have selected sites from across the U.S. and Canada as another strategy for increasing demographic diversity. In addition, the LOFT-HF study will utilize diverse recruitment practices including IRB-approved print and electronic versions of recruitment posters, pamphlets, letters, and other study promotional advertisements that can be disseminated in research and clinical offices and other applicable public spaces and via mail, email, website, patient medical record applications, TV and/or radio.

In addition to patient engagement training, we will offer a participation stipend in order to enhance retention. The study will require four in-person or remote study visits including the initial screening visit in which patients elect to complete an overnight sleep test if needed and three 1-hour in-person or remote visits at baseline, 6 month, and 12 month, as well as multiple phone follow ups. Participants can receive check-in by telephone, email and/or text messaging in order to maximize retention. Text messaging will only be utilized with participants who agree to receive text messages. We will offer a participation stipend. Patients will receive research participation stipends at various visit milestones: $50 for each in-person visit or remote data collection visit and $20 for phone follow-up. The average total stipend of $340 is justifiable reimbursement to compensate patients and for an average of 15 hours of study time, as well as associated travel times in the region. We anticipate this will increase enrollment without introducing selection bias and will improve retention in the study.

Recruitment and retention statistics will be posted in real-time on a study web site, including graphs that show deviations from projections. Sites that fail to meet projections for 2 consecutive months will be asked to provide a report with an analysis and action plan to the Steering Committee. If continued lags are observed, Drs. Williams and Redline, in consultation with the Steering Committee and DSMB/NHLBI, will determine further actions, which may include replacement of the site.

11. Statistics

11.1. Description of Study

LOFT-HF is a Phase 3, multicenter, randomized, double-blind, sham-controlled outcomes trial with parallel group design, with patients randomized to either control (optimal guideline based medical treatment [GDMT] plus sham NOXT) or active treatment (optimal GDMT plus NOXT)

in a 1:1 ratio. The primary objective is to evaluate the long-term effects of NOXT on the mortality and morbidity of patients with stable heart failure with reduced ejection fraction (HFrEF), already receiving optimal GDMT who have central sleep apnea (CSA). The secondary objectives are to evaluate patient-reported outcomes (disease-specific and generic quality of life); disease-specific mortality; and cardiovascular events. Subgroup analyses are planned to identify which patients treated with NOXT benefit most based on physiological endotypic traits. Adults, ages 21 years and older, with HFrEF and CSA who meet study eligibility criteria, will be recruited from approximately 50 well-established cardiovascular medicine/sleep centers, and further evaluated with sleep studies to identify the presence of CSA. It is anticipated, based on the literature and our experience conducting similar screening, that about 35% of participants will be eligible after PSG. Approximately 2,450 patients will be recruited to undergo PSGs to randomize a total of 858 patients (429 per arm). Participants will undergo standardized assessments including anthropometry, blood pressure, and questionnaires at baseline and at 6 and 12 month follow-up in-person or remote visits. Telephone calls will be conducted at months 1, 3, 9, and every 6 months after the 12 month visit until the last participant has completed his 12-month visit. Adverse events, hospitalizations and vital status will be collected over the entire intervention period. Given a 3.5 accrual period, mean follow-up time is estimated at 2.5 years (max 4.5 years).

11.2. Statistical Analysis Approaches

Primary analyses will follow the “intention-to-treat” principle; that is, individuals will be analyzed according to their assigned treatment group, whether or not they receive the study treatment as assigned. Every effort will be made to obtain follow-up data on all randomized subjects, whether or not they follow their assigned treatment. Preliminary Analyses

Our approach will involve close collaboration between clinical experts (on the Steering Committee and Scientific Advisory Committee) and biostatisticians, while ensuring appropriate blinding. Interim analyses of baseline variables (aggregated across intervention groups) will be conducted early in the study to ensure that the collected and derived data follow the assumed distributions, and that appropriate methods for identifying outliers and for computing clinical scores are implemented. Reports will provide a full description of the distributions of each study variable, along with indices of associated data quality, and include graphical displays. The amount and patterns of missing data, if any, will be characterized. Measures that are not normally distributed may be transformed to meet model assumptions. Before conducting final analyses, descriptive statistics will be generated using the total data set, ensuring that outliers or potential discrepancies in the data are resolved.

11.2.1. Descriptive Comparisons between Treatment Groups at Baseline and Over Time

Descriptive analyses will be performed to characterize the treatment groups, and to confirm that the randomization resulted in no important group differences at baseline. Study endpoints, dropout rates, cross-over rates, and patterns of missing data will be described. Graphical methods such as stem-and-leaf diagrams, boxplots, and scatter plots will be used to examine distributions, and guide the choice of transformations.

11.2.2. Statistical Approaches to Testing for Treatment Differences

The primary analysis is in the intention-to-treat population that consists of all patients randomized. The primary study endpoint is the time to first event (all-cause death, HF-related hospitalization, life-saving CV procedure), as assessed by the CEC. The primary analysis will

use a Cox proportional hazard model relating the primary outcome and treatment indicator, adjusting for the stratification factor.

The null hypothesis (H0) is: The distribution of time to first event in the intervention group is identical to that in the control group. The alternative hypothesis (H1) is:

The distribution of time to first event in the intervention group differs from time to first event in the control group.

11.2.3. **Secondary Analyses**

While our primary analysis focus on time to first event, we will collect data on all events occurring during follow-up and conduct recurrent event analyses.

In secondary analyses, we also will compare the effect of sham NOXT vs. NOXT on secondary endpoints including patient-reported outcomes; exercise capacity; disease-specific causes of re-hospitalization and death; and cardiovascular events.

Secondary analyses are considered exploratory and will be tested at significance level of 0.05 without adjusting for multiple comparison. Secondary endpoints will be analyzed according to type of scale. Time-to-event endpoints will be analyzed analogously to the primary endpoint. To assess the treatment effect on time to first HF-related hospitalization and CV mortality, mortality from other causes will be treated as a competing risk. Cause-specific cumulative incidence functions, instead of the standard Kaplan-Meier method, will be used to describe the probability of event occurring over time. Treatment effect will be quantified by cause-specific hazard ratios, obtained from Cox regression models, and care will be taken in interpreting the resulting HRs as among those who did not yet experience the event of interest or a competing event. Categorical variables will be analyzed using Fisher's exact tests or chi-square tests. Continuous endpoints will be compared using Wilcoxon rank-sum tests. Generalized linear models will be fit to assess the treatment effect on various endpoints adjusting for covariates for continuous, dichotomous or count data. Cox proportional hazard models will be used for time-to-event endpoints.

11.2.4. **Subgroup Analysis**

We will identify factors that moderate study outcomes in response to NOXT. The potential effect modifiers we will test and analysis methods are pre-specified in the Statistical Analysis Plan.

11.2.5. **Interim Analyses**

The study will be monitored routinely for issues of data quality, study conduct (including recruitment and follow-up rates), and adverse events. Monthly reports addressing these issues will be provided to the Executive Committee (aggregate [blinded] data). Reports will be provided to the DSMB and NIH every six months or more frequent as requested. We will monitor our primary outcome in planned interim analyses of safety, efficacy and futility.

We plan to perform two interim looks when roughly 30% and 60% of events have occurred. With the proposed design, a total of 520 events are expected and the first interim review for efficacy and futility would be scheduled to occur after approximately 156 primary endpoint events have been observed. It is estimated that this will occur approximately 24 months after enrollment starts, at which time, about 57% of subjects have been enrolled into the study with average follow-up time about 12 months. The second interim review would be scheduled after approximately 312 primary endpoint events have been observed. It is anticipated that the second interim look will occur around 36 months since the initiation of enrollment.

For futility monitoring, we will apply the inefficacy monitoring rule of Freidlin, Korn and Gray (Clinical Trials 2010; 7: 197-208) with a conservative boundary LIB0. For both interim reviews, the LIB0 conservative boundary would suggest stopping the trial for inefficacy if the oxygen arm had a hazard ratio >1.0 compared to the control arm. The Freidlin, Korn, and Gray approach will result in a trivial loss of power and requires no sample size adjustment.

For interim efficacy analyses, we will use the method of Haybittle and Peto. To create a formal framework for assessment of interim results, we will use the Haybittle-Peto boundary. That is, interim results for comparisons of the mortality and HF-related hospitalization rates between treatment groups will be considered sufficient to consider early termination only if the between-group differences are statistically significant at significance level of 0.001. The Haybittle-Peto stopping rule allows the final analysis to be evaluated at a 5% level of significance. As we do not anticipate that the interim analysis will yield efficacy data sufficiently compelling to require early termination, the Haybittle-Peto boundary is particularly suited for this situation.

Interim reports (open and closed) will be generated every 6 months (or more often as requested) including information on recruitment, baseline characteristics, data quality and availability, protocol deviations, and adverse events. Expected and actual number of randomized subjects and cumulative number of events will be reports and reviewed to ensure that recruitment is on target and the observed event rate is consistent with the assumed event rate.

At 18 months following randomization (or when approximately 43% of enrollment goal will be met), we will conduct a blinded sample size re-estimation using accumulating aggregate data to re-estimate nuisance parameters that have an impact on the power calculation of the trial. A comprehensive simulation study will be conducted to determine the impact of increasing the sample size and/or follow-up time on study power and overall type I error. The simulation study will be designed to mimic the LOFT trial as closely as possible and make use of the observed rate of early termination from the study and the overall event rates for all study participants, but will be blinded to the observed treatment arm-specific event rates and the difference between them. The overall observed event rate and its 95% confidence interval will provide a range of event rates that might be expected for the duration of the trial. The treatment arm specific event rate will be calculated based on the planned 20% reduction in

12-month event rate and the observed overall event rate. We will consider the following various scenarios including: 1) the originally planned study design; 2) additional year of follow- up after 858 participants are accrued. Additional scenarios may be included if deemed necessary upon discussion of the investigation team, the DSMB and the funding agency. The estimated power for different scenarios will inform the decisions on whether or not additional participants and/or follow-up time will be needed.

Interim comparative data will be considered confidential and will be available only to the DSMB members and to the DCC statistician/unblinded DCC staff analyzing the interim data and preparing the DSMB report. Concurrence with the monitoring plan by the Steering Committee, the DSMB, and the NIH will be required prior to implementation of the plan.

We hypothesize a 20% reduction in the 1-year composite event rate, which is high enough to change practice. This effect is within the range of that observed across intervention studies (ranging from 35% for cardiac resynchronization therapy and beta blockers to 15% to 25% for other medications). We anticipate a 1-year event rate of 40% in the control group based on the HF literature showing that patients with advanced HF will experience annual morbidity and

mortality event rates of approximately 40% or greater, especially in the setting of co- morbid CSA.

A total sample of 858 subjects (429 in each arm) achieves 87.9% power at a 5% significance level to detect a hazard ratio (HR) of 0.755 when the 1-year event rate in the control group is 40%, using a two-sided logrank test. We assume a 5% cross-over throughout the study and 10% loss to follow-up throughout the study, and a Cox model with exponential distribution (assuming constant hazard rate), and a 2.49 average length of follow-up.

Original and Revised LOFT-HF Patient Accrual

	Original*	Revised$		
Accrual end date	Jan 31, 2023		Jan 31, 2024	
Additional Follow-up Period	12 months	6 months	9 months	12 months
Average length of follow-up	2.75 years	2.49 years	2.74 years	2.98 years
Power	**90.2%**	**87.9%**	**89.8%**	**90.4%**

*: Corresponds to calculations provided in the original study protocol. Assumes the accrualpattern is uniform over 3.5 years.

$: Based on the revised projected accrual pattern allowing a slower accrual during siteactivation.

11.3.**Sample Size Calculation**

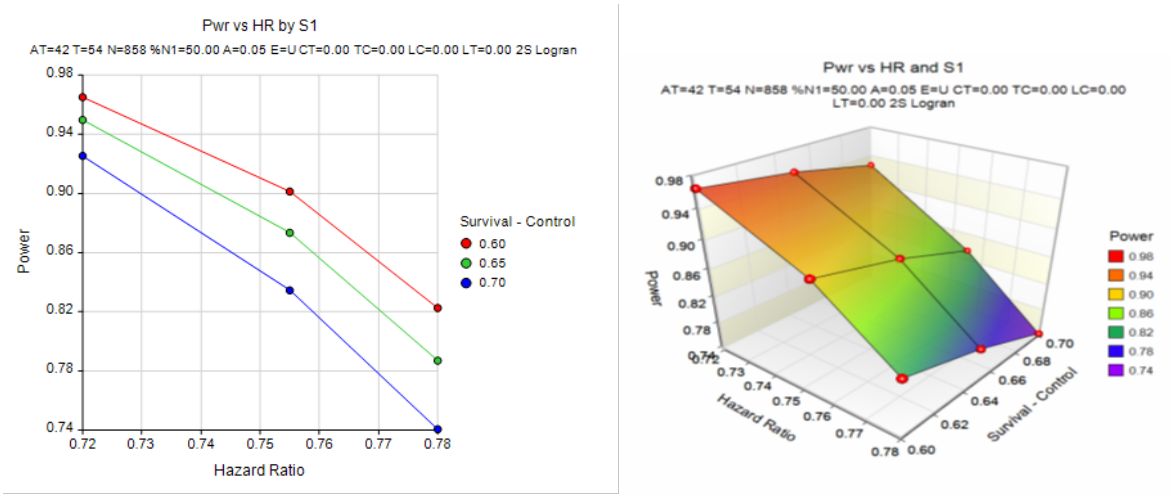
We hypothesize a 20% reduction in the 1-year composite event rate, which is high enough to change practice. This effect is within the range of that observed across intervention studies (ranging from 35% for cardiac resynchronization therapy and beta blockers to 15% to 25% for other medications [47,48]). We anticipate a 1-year event rate of 40% in the control group based on the HF literature showing that patients with advanced HF will experience annual morbidity and mortality event rates of approximately 40% or greater (71,72), especially in the setting of co-morbid CSA (18,19). As described in the CCC application and Protocol Draft, several design strategies will be employed to enrich the risk of the enrolled patients. We will not use a run-in design that would select samples with better prognosis.

A total sample of 858 subjects (429 in each arm) achieves 88% power at a 5% significance level to detect a hazard ratio (HR) of 0.755 when the 1-year event rate in the control group is 40%, using a two-sided logrank test. We assume that an accrual period of 4.5 years with a slow ramp up until the end of May 2020, then uniform across the remaining recruitment period until the end of January 2024, and that the study will last until the last enrolled subject completes six-month follow-up. We further assume that the drop-out rate and cross-over rate during the study period are 10% and 5% respectively for both treatment groups.

Conservatively assuming that 35% will screen positive will require screening a total of 2,450 subjects.

We performed sensitivity analyses for power analysis based on varying assumptions of effect sizes (HR=0.72, 0.755, and 0.78) and 1-year event rates in the control group (30%, 35%, and

40%), assuming the same rates of losses to follow-up and cross-over. As shown in the Figure, the proposed sample size achieves over 80% power for most of these settings.



Power for varying effect sizes and 1-yearcontrolevent rate (1-Survival).
AT=Accrual Time (in Months); T=Total Time (in months).

Our sample size also provides adequate power for key secondary endpoints. Using two-sided tests at 5% significance level, a sample size of 858 provides 80% power to detect 0.2 SD difference in means for a continuous endpoint using a two-sample t-test; to detect a 35%, 23%, and 16% reduction in risks when the risk in the control group is 20%, 40% and 60% for a binary outcome using a Z-test with pooled variance.

12. Access to source data/documents

The investigator will permit study-related monitoring, audits, IRB/IEC (Independent Ethics Committee) review and regulatory inspections, providing direct access to primary patient data (i.e. source data) which supports the data in the eCRFs for the study, i.e. general practice charts, hospital notes, appointment books, original laboratory records etc. Because this enters into the realm of patient confidentiality, this fact must be included in the Informed Consent Form to be signed by the patient.

12.1. Source Data

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

12.2. Source Documents

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, electronic patient records, laboratory notes, memoranda, patient diaries or evaluation check lists, sleep study records, pharmacy dispensing records, recorded data from automated instruments, copies or manuscripts certified after verification as being

accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, records kept at pharmacy, at the laboratories and at medico technical departments) involved in this clinical study. In case of data that are collected while speaking to the patient and not documented as part of normal clinical routine, the e-CRF is the source document, if the patients answer is documented there without prior documentation on paper.

12.3. **Direct Access**

Direct access is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party (e.g. domestic and foreign regulatory authorities, the Sponsor and/or authorized representatives of the Sponsor such as monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and Sponsor proprietary information.

13. Study Coordination and Data Management

The CCC will be based at OSU. It will be responsible for finalizing the informed consent templates (along with input from the DCC and overall study leadership and SAC), navigating central IRB approval (including reliance agreements across entities), working with the DCC to design and implement the eCRFs, coordinating the clinical activities of each of the clinical sites, providing key input into medical safety monitoring and central adjudication of treatment failures and adverse events, and monitoring and driving enrolment. The CCC leadership and the CCC Program Manager will interact regularly with site personnel to promote enrolment, using the many techniques described in Section 10.3, and leverage the RROS in meeting the enrolment milestones of the trial. CCC project management will directly support the needs of scientific study leadership (Executive Committee and Steering Committee) to identify barriers, make timely responses, and optimize the allocation of limited resources to meet the pre-defined study objectives.

The DCC will be based at the Brigham's and Women's Hospital Program in Sleep Medicine Epidemiology and Harvard Medical School. Its responsibilities include data management, study coordination, communications, statistical oversight, report generation, and data archival and dissemination. The DCC will be responsible developing and maintaining the database and study web portal; monitoring data quality and conducting data audits; supporting quality control; generating all case report forms; supporting study communications; designing; conducting the statistical analyses and preparing Steering Committee and DSMB reports; and creating final archives of study data for data dissemination. In collaboration with the CCC and other study investigators, the DCC will be responsible for preparing and maintaining key study documents (including training manuals and Manuals of Procedures [MOP]); and coordinate central training sessions and site visits.

A central Sleep Reading Center (SRC), based at Brigham and Women's Hospital, will provide centralized PSG support for the trial. It will develop all sleep training manuals, oversee the training and certification of site personnel on the use/administration of the portable sleep monitors, oversee sleep data quality, score the sleep studies, provide timely reports (within 2 business days) of parameters used to determine eligibility (central apnea hypopnea indices, obstructive apnea index, and CSR), identify urgent referrals from the sleep studies and report these to the clinical sites, and generate metrics of ventilation/airway function for use in predictive analyses. It will produce archives of the raw and scored data from data dissemination. The SRC also will be ensuring a protocol is in place to deliver, set-up, and educate participants on use of home oxygen; developing the final protocol for home

oxygen/sham oxygen use; will provide real-time monitoring of oxygen flow use; and communicate with the local clinical teams any need to reinforce adherence to oxygen. A central oxygen use adherence expert will support local staff in messaging and actions to help reinforce treatment adherence.

The Clinical Endpoints Committee (CEC) will be based in the Department of Cardiology, Brigham and Women's Hospital, Harvard Medical School. The CEC is responsible for unbiased and consistent endpoint review and adjudication of all investigator-reported and CEC-identified study endpoints, according to pre-specified endpoint criteria. The CEC will develop a manual of operations that defines the CEC process and expands on endpoint definitions, for use in the adjudication process. The Executive Committee will review and approve of the CEC manual of operations, prior to initiating the study.

The final version of this study protocol and corresponding MOP will specify the study design in sufficient detail to assure that the trial is conducted in a consistent and rigorous manner, including details such as procedures for: electronic data capture system and responding to queries, collecting and transmitting various types of data; adverse event ascertainment and reporting, reporting protocol deviations; and scripts/instructions for recruitment. The DCC will ensure that any study amendments, protocol updates, and versions are clearly labeled, and that revised information is distributed in a timely fashion to the CCC and each site.

The Data Management System (DMS), housed within a dynamic secure, HIPAA compliant, study web portal (Slice, built on Ruby-on-Rails), will provide data entry, integration, processing, and reporting services. Data will be captured through a variety of ways, including patient and staff direct entry of data into electronic tablets that present e-CRFs using a streamlined user interface. Data also will be received as electronic files (e.g., sleep studies, oxygen use records) and as pdfs (certain source documents). The backend relational database is PostgreSQL. In addition to on-line e-CRFs, the system will provide functionality for: tracking CRFs, data validation, query generation and tracking, and reporting. Data access is defined and tightly controlled according to each person's roles (blinded, unblinded). Advanced data filtering functions will ensure that staff have access to appropriate data while reducing likelihood of unblinding. The DMS will provide functionality for displaying a variety of real-time reports, graphs, and study documents required by key personnel and stakeholders to quickly view the status of the study and access procedure manuals and study materials directly.

A Central IRB based at Vanderbilt University will be used.

The Executive Committee will ensure that the study operations and milestones are congruent with the approved proposal. It will meet bi-weekly or monthly to review current and planned activities, relating these to milestones and operational plans, identifying study operations and communications that may require changes. It will identify areas for Steering Committee of Data Safety and Monitoring Board input.

The Steering Committee will provide overall study leadership, including overseeing all scientific and administrative aspects of the study, monitoring study progress and milestones, review the work of the subcommittees and provide input to their work and approve publications, presentations and ancillary studies. The Steering Committee will be responsible for all key study decisions with decisions made by majority vote. It will review the reports and work of all subcommittees, be responsible for responding to input from the DSMB and NHLBI, and ensure that all study decisions and study updates are communicated to the larger LOFT-HF Study Group through emails, portal newsletters, and direct contact as needed. The

Steering Committee will be co-led and co-managed the CCC and DCC PIs. It will also include representation of key Subcommittee Chairs and study site representatives.

The RROS will consist of diverse representatives from the clinical sites, including study coordinators. It will meet monthly to discuss strategies for optimizing recruitment and retention and oversee overall flow of the clinic examinations, data collection, and participant interactions.

13.1. Quality Control

Quality Control is defined as the operational techniques and activities, such as monitoring, undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled.

Quality Control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

A data quality control process will be implemented that addresses all stages of data handling, from data capture to analysis. First, all procedures will be specified in the Final Protocol and MOP to allow for unambiguous use in the study. A central training session and subsequent site visits will be held to ensure that personnel understand the study's goals and objectives, data collection process, adverse event collection, database software, and all applicable standard operating procedures. Key procedures (e.g., survey administration, adverse event identification, distribution of oxygen concentrators, data entry and transfer, sleep apnea testing, and blood pressure measurement) will require certification of staff prior to their use with study participants. Requirements differ per procedure, but may include documentation of successful performance during central training, completion of a written exam, and submission of successfully completed pilot studies. After initial certification, each research staff's performance will be monitored on an ongoing basis. If submitted studies fall below threshold levels for quality, the site PI will be notified and procedures for remediation will be implemented (e.g., re-training, or removal from the study).

Second, a subject registration procedure will be used that checks eligibility criteria prior to assigning a randomization code, minimizing the likelihood that ineligible participants are randomized.

Third, data accuracy and completeness is optimized through easy to use electronic interfaces that provide dynamic feedback during data entry or survey (e-CRF) completion regarding implausible values or skipped fields. Forms require all items to be completed before each is closed. A sample of data will be entered a second time using a web-interface that requires on-line resolution of conflicts between data values being entered for the second time and first data entry values. Each conflict will be documented in an audit report that will provide feedback for summarizing and tracking the accuracy of data entry. Furthermore, all incoming data will be checked to assess the accuracy and the completeness of electronic reports. Data are validated through checks on variable formatting, range-checking (minimum/maximum values), and logic checks (skip patterns, etc.). Queries will be made of the full spectrum of study data: those directly entered and those electronically transmitted, including those from the Sleep Reading Center and CEC. Queries will be run on a weekly schedule. For key variables, or those prone to coding or collection errors, additional data checks will be established, such as the creation of graphs showing relationships between variables (e.g., height vs weight). The DMS will send queries to study coordinators that include the time frame when its resolution is expected.

13.2. Study Monitoring

Clear benchmarks for ensuring compliance with the study protocol, including adherence to regulatory and privacy requirements; recruitment and retention milestones; and targets for data completeness and data integrity will be established and monitored over the course of the study. If given sites or staff member exceed thresholds, appropriate retraining or remediation will be initiated.

13.3. Quality Assurance

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed and the data are generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements.

Using study milestones, the Executive and Steering Committees will regularly review graphic and tabular displays of randomized individuals by site and week, as well as breakdowns of screened, consented, eligible, and randomized subjects along with key demographic data. Pareto event graphs and other quality assurance tools will be deployed to provide feedback and assist with analysis.

13.4. Inspection

An Inspection is defined as the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authorities to be related to the clinical study and that may be located at the site of the study, or at the Sponsors and/or clinical research organization facilities or at any other establishments deemed appropriate by the regulatory authorities.

13.5. Audit

An audit is a systematic and independent review of study related activities and documents to determine whether the validated study related activities were conducted and the data were recorded, analyzed and accurately reported according to the protocol, designated Standard Operating Procedure (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements. An independent audit at the study site will take place within 3 months after recruitment is begun. Additional audits may take place at any time during or after the study. Audit results will be shared with the Steering Committee, relevant QA committees and other study personnel, and the DSMB. If data quality or procedures do not meet pre-specified thresholds, remediation, including additional training, or changes in procedures will be implemented.

All data operations and modifications will be recorded to a Data Audit Trail which will specify detailed information related to the types of data operations performed, by whom these operations were performed, date and time of operations, and data values modified.

14. Ethical and Legal Considerations

The respect for the rights of the patients will be guaranteed in each phase of the study in accordance with the Declaration of Helsinki and its current revision. The trial will be conducted in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP), Investigational Device Exemption (US federal regulations, CFR Title 21, part 812) regulations and requirements and ISO 14155.

14.1. **Ethical Considerations**

Trained research personnel who have completed necessary certification for human subject research will screen the targeted clinics (medical records) to identify and recruit potentially eligible patients, contact referring physicians to ascertain study eligibility and assure that HIPPA requirement are met, obtain informed consent, and confirm further eligibility criteria at clinic encounters and by telephone. Study PIs will perform a history and may elect to complete a physical examination to further assess eligibility.

Consent from the participant will be obtained at the time of study entry by trained study coordinators or a study investigator. All aspects of the study will be explained in detail. Before being entered into the study, each patient will sign an informed consent form that has been approved by the central Institutional Review Board. They will be informed of the nature of this research, its potential benefits and possible risks. They will be informed that they are free to refuse participation or to withdraw from the study and that this will not affect any future medical care.

The general procedures to be followed are:

- Participant who are potentially eligible (i.e., by diagnosis, echocardiography findings, hospitalization history, lack of comorbidities) will be identified by electronic records or review of medical charts.
- Prior to the scheduled screening visit, referring physicians will be contacted to confirm appropriateness of study participation for each potential participant and to agree to allow study personnel to contact the family.
- Potential participants will be contacted by telephone, mail or in-person (before hospital discharge, while at a clinic appointment), with arrangements made for a subsequent full screening visit, or for a follow-up interview if needed. The study will be described and written informed consent obtained.
- At a screening visit, an interview will be administered to assess eligibility criteria. A physical examination may be performed at the discretion of the PI to further assess eligibility criteria.
- Potentially eligible participants (after initial screening) will be provided with a home sleep monitor to use for one night unless a recent clinical sleep study is unavailable. If the sleep monitor shows that criteria for CSA are met, the participant will be invited to a full baseline visit and then will be randomized. If a clinical sleep study is available, that study will be transferred to the SRC for centralized scoring and eligibility assessment.

More specific approaches to the consent process: At the time of enrollment, discussion of the protocol and written consent for the research will be obtained by trained research coordinators or study investigators (who have been ethics committee certified). Consent forms explain in a lay persons' terms the nature of all procedures. It is stressed that participation is voluntary. The research assistant and PI are available to answer questions. The study PI (or his/her designee) will also meet and examines each participant at the time of the screening or baseline visit. The investigators will also be available to answer questions about the study at other times.

Across sites, common elements of the consent forms will include:

- Introduction/purpose that briefly explains what the research is studying and what the potential participant is being asked to participate

- Study procedures – what the participants will experience in their participation, what is standard care and what is added because of research participation, duration of the study and number of visits involved.
    - Screening procedures to determine if the subject can participate
    - Randomization/Study Intervention (full discussion of oxygen; health education)
    - Duration and number of visits using subheading for each visit type
    - Procedures performed at each visit
    - Follow-up procedures (phone calls) and procedures; what will occur and time involved
    - Description of procedures for discontinuation, including the participant's right to withdraw
    - Risks
    - Benefits
    - Alternatives to participation
    - Financial information
    - Confidentiality
    - Research related injury
    - Termination of participation
    - Summary of rights as a participant in a research study
    - Disclosure of study records
    - Contact information

Published data will not include patient identifiers.

14.1.1. **Central Institutional Review Board (IRB)**

Regulatory oversight of the LOFT-HF study will be administered by a Central Institutional Review Board (IRB) through one of three Trial Innovation Centers (TICs), a component of the Trial Innovation Network (TIN), (Duke University / Vanderbilt University). We intend to leverage these institutions' collective, extensive experience in the facilitation of quality and efficient regulatory oversight. The OSU CCC will submit an application to the TIN during the UG3 phase soliciting one of the TICs to serve as the IRB of record for participating clinical sites. TICs utilize the SMART IRB platform. The CCC has an existing SMART IRB reliance agreement and will partner with the TIC IRB to secure IRB authorization agreements with all sites using the SMART IRB platform. As the IRB of record, the TIC IRB will be responsible for conducting the review of the LOFT-HF protocol in accordance to 21 CFR Parts 50, 56, 312, and 812, 45 CFR 46 and applicable international and local regulations and laws with respect to the initial review, continuing reviews, and any potential modifications to the protocol. The TIC IRB will review reported adverse events, unanticipated problems involving risks to subjects, and any incident of serious noncompliance in accordance to the IRB's defined policies and procedures. All research –related documents will require TIC IRB review and approval prior to use. The TIC IRB will operate in a transparent manner, readily providing IRB meeting minutes to sites per requests and investigators and sites will be notified in writing of all IRB decisions.

The OSU CCC Project Manager (PM) will be responsible for communication across sites and ensuring each site is provided with IRB-approved versions of study documents. Other CCC PM duties will include notification of site research teams of TIC IRB determinations and communications, maintaining records of education and human subjects research training of investigators and research teams, and obtaining information related to potential variations in study conduct for purposes of evaluation of the local context by the LOFT-HF Executive Committee. The OSU CCC will work with the TIC IRB to release study records if needed for an audit by the relying sites' institutions or other regulatory agencies.

14.1.2. **Clinical Endpoints Committee (CEC)**

The CEC will be responsible for unbiased and consistent endpoint review and adjudication of all investigator-reported and CEC-identified study endpoints, according to pre-specified criteria, blinded to treatment assignment. Event review and adjudication will be performed in compliance with all Institutional guidelines as well as all other applicable FDA regulations and ICH E6 guidelines concerning the conduct of human subject research. In addition to the study-specific MOP, the CEC uses center-wide CEC Policies and Procedures (P&Ps) that serve as the backbone to all key components, processes and functions of the CEC.

The general approach for CEC adjudication entails: a) Each event will be independently reviewed by two physician reviewers with expertise in adjudication of CV events in clinical trials; b) The CEC project management staff will be responsible for assigning and distributing events to physician reviewers and scheduling adjudication committee meetings with the CEC Chair. c) The Committee will receive and adjudicate endpoints via Committee on a regular, consistent basis (i.e. daily and weekly activity) to avoid back logs in events receipt and adjudication.

The specific procedures entail: The CEC will adjudicate all potential primary and secondary endpoints (see Protocol and CCC Application). It will be responsible for providing clear, concise, and thorough internal documentation of the key event details and rationale for event adjudication. The CEC will receive electronic source documents from sites for each potential event via an on-line portal. Project management staff will assign the electronic dossiers to 2 physician reviewers, maintain a database to track these assignments, and will be responsible for CEC-generated queries, resolving them with the site, and forwarding appropriate responses back to the physician reviewers. Relevant information will be documented on the Event Review Form (ERF) completed by each physician assigned to the event. There will be one final adjudication form completed and signed by both physician reviewers assigned to the event and an administrative staff person responsible for ensuring that the form has been completed in a clear and thorough manner. Once an event has been reviewed in Committee and an adjudication has been reached, the ERF will be finalized and signed, with the final adjudication entered by the chairman into the electronic database system.

14.1.3. **Data and Safety Monitoring Board (DSMB)**

The NHLBI will establish an external DSMB according to NHLBI policies. The members will include experts in heart failure, sleep medicine, biostatistics, clinical trials, and ethics (some overlapping). The DSMB will convene to review the final protocol and DSMB Charter before study initiation and then periodically, and not less frequently than annually. The DSMB Chair will receive all reports of unanticipated serious adverse events in real time. The DSMB will receive interim reports every 6 months for the DSMB call/meeting. At each meeting they will determine whether study progress, data integrity and safety monitoring warrant continuation of the study and will recommend the study to continue or be terminated, accordingly. They

also approve the data safety plan before the study is begins. Duties of the chairperson: The chair will lead the scheduled board meeting and review the prepared board meeting minutes.

DSMB Meetings and Recommendations: Meetings will require a quorum. All members will be responsible to read the submitted DSMB reports. The chairperson will lead the discussion. Duties of the board will include evaluation of the progress of the trial, including assessment of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome. Monitoring will also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study.

Potential motions of the board meeting include recommendations for either of the following:

a. Study continuation; no change required

b. Study continuation with stipulation to be formally addressed and approved by the DSMB chair

c. Study suspension with stipulation to be formally addressed and approved by the DSMB prior to resumption

d. Study termination

The DSMB's summary report will be reviewed and finalized by the chairperson. The report will then be communicated to the NHLBI who will communicate recommendations to the DCC and CCC. DSMB recommendations will be communicated to the IRB in the context of the continuing review process. It is the responsibility of the PI to ensure that the IRB is notified by motions requiring termination or suspension of the trial.

DSMB Report and format: An interim report will be prepared for each meeting by the BWH DCC, supervised by the study statistician, Dr. Wang. The DCC will propose a draft report format to be finalized at the first DSMB meeting. Adverse event reports will follow NIH recommendations (http://www.nhlbi.nih.gov/funding/policies/dsmpolicy.htm).

14.2. **Modification of Protocol**

The Steering Committee, DSMB and NHLBI will be required to approve any changes to the protocol. Changes will be clearly documented, including dates of the change. All materials will be maintained using version controlled identifiers, minimizing likelihood of using outdated materials.

14.3. **Personal Data and Data Protection**

All staff will have completed certification in The Collaborative IRB Training Initiative (CITI) program.

All information will be kept strictly confidential and used for research purposes only. Records will be identified by a subject id and visit number rather than the subjects' name, and will be secured in locked files. Attempts will be made to minimize the possibility of linking such data to personal identification information by restricting access to personal identification information to the study coordinator, with such information (names, addresses and identification numbers) stored separately from other data in locked files, and computers secured appropriately. Data will be transmitted electronically as encrypted files via secure FTP protocols. The DCC will not receive identifying data nor PHI other than dates of events, except in cases where participants need to

receive timely shipments of study therapy supplies. The DCC may receive PHI (name, mailing address, phone number) so replacement therapy supplies (cannulas, tubing, etc.) may be shipped directly to study participants. As soon as the shipment is placed, the address/identification information will be destroyed securely (and this information will not be stored physically or electronically). Study-wide data will be stored at the Brigham and Women's Hospital DCC computers that are located in a restricted access research suite; computer information is protected by use of passwords and a firewall. All DCC web and database servers are secured within the Partners Corporate Datacenter and behind the Partners Information Security firewall. They comply with all Partners Healthcare Information Security policies, developed and maintained by the Partners Chief Information Security Officer, for authenticated, secure and minimum access. All systems are patched, monitored and scanned routinely for vulnerabilities and intrusions by the systems administrator and PHS Information Security. Data is encrypted, where applicable, in compliance with state and federal government standards, regulations, and in accordance with Partners Security and Privacy policies. All configuration changes that could affect accessibility or security are approved by management.

14.4. Data Handling and Record Keeping

All NHLBI requirements related to study close-out will be followed. At a predetermined termination date, all computerized, non-database files and, minimally, a complete database table transfer to CSV files will be archived to a suitable media format. The format of the archive media will be a standard format to ensure reliable restoration of any project file(s). All non-computerized project data will be packaged and documented to ensure that the project package and related archived media will be available for future queries about the project. The DCC will coordinate retention and transfer of documents with the PIs and the sponsors, and also will disseminate data through BioLINCC and the National Sleep Research Resource, as described in the Resource Sharing Plan.

14.4.1. Completion of Case Report Forms

All medical data in this trial are to be recorded directly in the eCRFs. The investigator must ensure the accuracy, completeness, legibility and timeliness of data. Built in features will provide checks for completeness as well as logic and range checks.

14.4.2. Archiving

Reports will be created and posted on secure areas of the study portal to provide ongoing feedback to the Steering Committee, DSMB, NIH, and each site regarding outstanding tasks and the quality of data already entered (i.e. counts, completeness, missing data).

15. Final Report and Publication Policy

To be finalized by Publications and Presentations Subcommittee and approved by the Executive Committee and Steering Committee.

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17. Signatures

The undersigned have read this protocol and agreed to conduct this study in accordance with all stipulations of the protocol and in accordance with the Declaration of Helsinki.

Date	Signature
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