Human Subjects Protocol

VA Puget Sound IRB

1 I01 HX003319-01A1

Pragmatic Obstructive Sleep Apnea Weight Loss Trial Assessing Effectiveness and Reach (POWER)

Funding Agency: HSR&D

Principal Investigator: Lucas M. Donovan, MD MS

March 04, 2025

Version 2.19

Summary of Edits:

Version 1.1, 8.03.2021:

- List of Abbreviations: Updated

5.0 Study Procedures

- Added JLV and Capri throughout this section as additional potential data sources

Version 1.2, 9.09.2021:

5.5.3 Secondary Effectiveness Outcomes:

- Added “global impression of change” measure and description

Version 1.3, 10.06.2021:

- Added summary of Edits section
- Added footer to include filename date and version number
- Updated Study Personnel-removed Peter Rise and Added Anna Pannick

Version 2.0, 11.26.2021:

Updates throughout protocol:

- Added USB as a mode for intervention course videos
- Added Qualtrics, online, and email as additional modes throughout protocol
- Corrected grammar and formatting throughout
- Replaced ‘D-ELITE’ with “lifestyle intervention”
- Removed guaranteed use of ANNIE texting

Abstract

  - Removed abstract template instructions

Section 2.0 Introduction

  - Corrected some grammar and updated cost of videos and added videos via USB
  - Reformatted, renamed, and/or moved tables and figures

Section 5.0 Study Procedures

- Added 5.3.4 Stratification section
- Added 5.3.6. Participant compensation section
- Added Qualtrics, online, and email for recruitment and survey administration

5.3.2. Medical Clearance

- Added sleep provider contact

5.3.3. Randomization

- Updated Lifestyle Coach training with current provider of training/certification: SparkPro

5.3.7 Participant compensation

- Added qualitative interview payment

5.4 Inclusion/Exclusion Criteria

- Changed the inclusion criteria of OSA to sleep provider confirmed
- Edited Table 5: Measures and timing of collection to include missing secondary outcomes

5.5.1 Baseline and follow-up effectiveness measures and data collection

- Added “global impression of change”

5.5.7.2 Data Collection for Qualitative Evaluations of Implementation Process
- Replaced audiotaping orientations with auditing
- Removed guaranteed use of ‘clockify’
- Renamed section to distinguish from analysis

5.5.7.3 Data Collection for Quantitative Evaluations of Implementation Process
- Renamed section to distinguish from analysis
- Revised content for clarity

5.6.2 Hypothesis Testing for Analysis of Trial Population

- Edited analysis precision variables to reflect new stratified randomization covariates

5.6.4 Analysis for Qualitative and Quantitative Evaluations of Implementation Process

- Merged former separate quantitative and qualitative sections
- Renamed section to distinguish from data collection
- Revised content for clarity

6.1 Safety Assessment

- Generalized investigator(s) assessing AEs

7.0 Privacy and Confidentiality

- Added info re: option to answer questionaries online via Qualtrics
- Added info re: contact information shared with contracted sleep study company

9.0 Information Security and Data Storage/Movement

- Added info re: type of information shared with Qualtrics
- Added info re: how Qualtrics data will be stored in SQL database
- Added info re: transferring data from a contracted company performing home sleep apnea testing

Version 2.1, 01/18/2022:

Updates throughout protocol:

- Corrected grammar and formatting

- Removed “random” or “randomized” description for sleep study

1.0 Study Personnel

- Added Travis Hee Wai

5.2.5 Research Invitation

- Added contingency plans for completing screening survey

5.3.2 Medical Clearance

- Updated asking clearance from sleep specialist for a single night

5.3.3 Randomization

- Added that participants may be notified of randomization via email

5.5.1 Baseline and follow-up effectiveness measures and data collection

- Added Qualtrics survey adaptations

5.5.2 Primary Outcomes

- Included validation response for weights reported in Qualtrics

5.5.6 Physiologic OSA Severity

- Removed the sleep study from baseline. Increased n=100 to n=200 per arm at 12 months.

Version 2.2, 02/18/2022:

Updates throughout protocol:

- Removed gender as a stratification variable, reducing the total strata from 16 to 8

Table 5: Measures and timing of collection

- Increased n=200 to n=400 for total HSAT collection.

7.0 Privacy and Confidentiality

- Added info re: incoming emails or text messages to the POWER inbox
- Added info re: outgoing text messages

5.2.5 Research Invitation

- Removed Qualtrics screening survey

5.3.7 Participant compensation

- Added sleep study participation as a qualifier for compensation

5.6.2. Hypothesis Testing for Analyses of Trial Population

- Modified models for testing our hypotheses

5.6.3. Missing and Misclassified Data

Added more practices for missingness

Table 4: Inclusion and Exclusion Criteria

- Added participation in other intervention studies and inability to speak, read, or understand English under exclusion criteria

Version 2.3, 03/18/22

5.2.6. Recruitment of Lifestyle Coaches for Interviews

- Removed qualitative interview-specific information statement
- Edited language to reflect future modifications

5.4 Inclusion/Exclusion Criteria

- Modified reviewing sleep studies to include those that have not opted out

5.5.7.2. Data Collection for Qualitative Evaluation of Implementation Process

- Removed “by phone” as mode for all interviews to allow for more flexibility in interviewing, particularly with the lifestyle coach interviews.

Version 2.4, 06/03/22

Updated study staff-remove Tanya Nguyen

5.5.7.3. Data Collection for Quantitative Evaluations of Implementation Process

- Changes to REACH, EFFECTIVENESS, and Maintenance subsection defining REACH and how we will query EHR

Version 2.5, 07/28/22

Updated Study Staff – added Anthony Bais

Version 2.6, 08/24/22

5.2.4. Oversampling

- Added mailed re-invitation to women to bolster our 30% oversampling aim

5.4. Inclusion/Exclusion

- Clarification of exclusion criteria relating to weight loss programs, medications, surgeries

5.3.6.2. Format, Structure, and Content:

- Removed reference to inclusion of VA resources for cooking classes and shopping.

5.5.7.3. Data Collection for Quantitative Evaluations of Implementation Process:

- Fidelity section updated re: audits of intervention orientations and lifestyle coach communications

Version 2.7, 12/5/22

Updated Study Staff-Gebremariam, Nathnael S.

5.2.5 Research invitation

- Added option to remail/email to all nonresponders two weeks or more after initial mailing/emailing

5.2.6 Recruitment of Lifestyle Coaches for Interviews

- Changed from interview to focus group for qualitative lifestyle coach assessments

5.5.6. Physiologic OSA Severity

- Added procedure should home sleep study tests reveal concerning results
- Also added specifics re: 3% and 4% saturation values in reports
- Added details re: $25 compensation for HSAT participation

5.5.7.2. Data Collection for Qualitative Evaluation of Implementation Process

- Changed Lifestyle Coach qualitative evaluations from interview to focus group
- Added details re: $25 compensation for interview participation

5.5.7.3. Data Collection for Quantitative Evaluations of Implementation Process

- Edited costs and budget impact analysis section to more clearly and accurately explain our proposed analyses.

Version 2.8 02/22/2023

Abstract

- Updated ‘progress to date’ section to reflect that recruitment began 4/4/2022

5.1. Study Design

- Updated figure 4 to align with study procedures. Specifically, we do not e-mail sleep providers prior to initial enrollment (See Section 5.3.2).

5.2.2 Recruitment

- Revised language to reflect the fact that recruitment has already begun.

5.2.3 Oversampling:

- Revised language to align with past as opposed to present tense.

5.3.2 Medical clearance:

- Revised to state that we will also contact primary care providers to discuss safety of the one-night sleep study.

5.4 Inclusion Criteria:

- Removed constraints around number of lifestyle coaches potentially involved in interviews. Instead, we will aim to interview all lifestyle coaches.

5.5 Study Evaluations

- Clarified timeline of compensation, in alignment with approved information statement.

5.5.1 Primary Outcomes:

- Clarified weight collection to align with outcomes currently registered with clinicaltrials.gov. The co-primary outcome of weight will include clinically measured weights identified from CDW. We originally planned to include self collected weights collected as a contingency. However, given the trajectory of the COVID-19 pandemic and clinic availability, we made the decision to only use clinical weights, and explore self-weights in in secondary analyses. Should clinical weight availability change as we enter primary outcome collection period, we may revisit this decision.
- Also clarified that self-weights are not measured at baseline, but shortly following randomization when intervention scales are sent.
- Updated Table 5 to align with changes above.

5.5.1 Secondary Outcomes:

- Added descriptions of self-reported nightly sleep apnea treatment adherence and sleep duration at baseline, 3, 12, and 24 months. These are currently being collected in IRB approved forms.
- Updated Table 5 to align. Also added reports of intervention participant self-monitoring and intervention adherence at 3 and 12 months which is documented in 5.3.6.4.

5.5.4. Monitoring for eating disorders:

- Added additional question to 3-month surveys about the development of eating disorders.

5.5.5 Physiologic OSA Severity:

- Added details around pre-test screening and practices.
- Clarified that we will conducting sleep studies among up to 200 participants per arm.

5.5.6 Fidelity assessments

- Peer audits of orientations will occur for *up to* 10 orientations per coach

5.6.1. Statistical Power for Primary Outcomes

- Added power calculations around a potential 3.3kg difference between groups, which approximates a meaningful ~3% change in body weight.

5.6.1. Data Analysis Plan

- Clarified language in hypotheses to align with language submitted to DSMB

- Added formal hypothesis (H2b) for comparing AHI between groups, as HSATs will only be collected at single point in time (12 months).
- We will now plan on using the ANCOVA model: Y = b0 + b1Y0 + b2X + b3Q + e as our primary analytic model.
- Added secondary subgroup analyses.

5.6.3. Missing and Misclassified Data

- Explicitly stated that we will test our hypotheses using a complete case analysis. (Previously this statement was implied by our language that imputation would be used in secondary analyses).

5.7 Withdrawal of Subjects

- Defined participants who are deemed to have been "lost to follow-up".

6.3.1. Adverse event monitoring

- Clarified ambiguous language around review of adverse events. Prior version could have been interpreted that PI and another clinician would *both* review each adverse event. The current version has been corrected to describe that PI or another clinician will review each adverse event.
- In consultation with co-investigator psychologist, Dr. Katherine Hoerster, PhD we added eating disorders to list of expected adverse events given high prevalence within the Veteran population (Mitchell et. al. Psychol Assess, 2021, PMID: 34292003).

7.0. Privacy and confidentiality

- Clarified that we only need to identify a participants carrier if we are sending text messages via e-mail.

Version 2.9 03/17/2023

5.3.7. Participant compensation

- We will offer additional compensation of $25 for completion of the 12-month survey outcome packet.

5.5.1 Baseline and follow-up effectiveness measures and data collection

- Added language to this section as well regarding compensation of $25 for completion of the 12-month survey outcome packet.

5.5.2. Primary Outcomes: Contingency Weights

- With the COVID emergency restrictions continuing to ease, we are decreasing patient burden by no longer requiring self-weights from all participants. Instead, we may ask for self-weights as needed in the case of missing data.

7.0 Privacy and Confidentiality

- Updated section on texting and Qualtrics to include sending batch texts through the Qualtrics platform

Version 2.10 5/16/23

5.5.1 Primary Outcomes:

- Added greater detail around the timeline for collecting clinical weight measures for the 24 month time period (18-24 months).

5.5.5. Physiologic OSA Severity

- Updated this section to include specifics re: contracted company, Sleep Care.
- Reduced overall max number of sleep studies to 250 overall (125/arm) due to budget constraints

5.6.1. Data Analysis Plan

- Revised primary and secondary analytic models to linear mixed effects model. This replaces our originally planned model of ANCOVA with complete case analysis. After discussion with our biostatistician, we decided to pursue a linear mixed effects model because it is valid under the missing at random assumption. (Note that no data has yet been analyzed, and we are just now collecting 12 month outcomes).
- Added greater discussion around how we will impute missing covariate data.

8.0. Communication

- Updated this section to include specifics re: contracted company, Sleep Care.

9.0. Information Security and Data Storage/Movement

- Updated this section to include specifics re: contracted company, Sleep Care.

Version 2.11 6/14/23

- Updated study staff list to add Ari Leonhard and remove Travis Hee Wei

5.0 Study Procedures:

- Advanced the focus of long-term outcome by 3 months (24 months to 21 months post-randomization). This change is made to allow uniform capture of longer-term outcomes in the funded timeframe of the study. For all outcomes (EHR & surveys), we will continue collection until participants are 24 months post randomization.

5.3.7. Participant compensation

- Addition of using gift cards to compensate participants

Version 2.12 7/10/23

- Updated study staff list to remove Nathnael Gebremariam

5.5 Study Evaluations:

- To reduce primary care burden, we are changing our reminders for those with missing clinical measures. In lieu of walk-ins, we will ask all participants with missing weights at 12 months to schedule visits for follow up weight measurements. We will not ask patients

to return for secondary outcomes including blood pressures or weights at the 21 month time period.

Version 2.13 8/14/23

5.3.7. Participant compensation

- Revised window for survey outcome collection from 21-month to 24-month with payment following 21-months.

5.5.1 Baseline and follow-up effectiveness measures and data collection

- Same as above, change from 24-month to 21-month for survey outcome collection and payment.

Version 2.14 11/22/23

5.5.5. Physiologic OSA Severity

- If a participant requests the results of their home sleep apnea test, a member of the study team will call them and review the results. We may also mail the report upon request

Version 2.15 01/11/2024

6.2. Data Safety and Monitoring Board

- Removed reference to sending DSMB charter when available as one is available now

Version 2.16 01/25/2024

6.3.1. Adverse event monitoring

- Updated adverse event chart review procedure for participants that do not complete a survey at 21-months post-randomization

Version 2.17 04/15/2024

6.3.1. Adverse event monitoring

• Updated adverse expected events to explicitly include death, in alignment with established Data Safety Monitoring Board analysis plan.

Version 2.18 07/02/2024

5.4. Inclusion/Exclusion Criteria & **5.5.2. Primary Outcomes:**

• Added details around how weights pulled from the electronic health record are reviewed for suspect or erroneous values.

Version 2.19 03/04/2025

1.0 Study Personnel

- Removal of Margaret Collins and Christian Helfrich from list of study personnel

6.3 Adverse event monitoring

- Added a comparison of hospitalization rate between arms through 24 months using data compiled from the CDW.

Abstract

1. Objective(s) and Hypotheses:
Our primary aim is to test the effectiveness of a proactively delivered and pragmatic weight loss intervention to improve co-primary endpoints of sleep-related quality of life and weight among Veterans with obstructive sleep apnea (OSA) and obesity. Secondarily, we will compare additional outcomes between groups: cardiovascular risk scores, sleep symptoms, and AHI. Finally, we will also conduct an implementation process evaluation informed by the RE-AIM framework to identify predictors and determinants of population uptake of the intervention, alternative guideline-based treatments for OSA and obesity, and the achievement of patient-centered outcomes.

2. Research Design:
We plan a hybrid type 1 pragmatic randomized controlled trial assessing effectiveness and an implementation process evaluation.

3. Methodology
We will proactively identify Veterans with OSA and obesity nationwide using data from the CDW (n=696), randomizing patients 1:1 to usual care plus the GLB weight loss intervention or usual care alone. We will collect primary outcomes at 12 months, but we will also collect outcomes at 3 and up to 24 months to assess trends over time. We will use quantitative and qualitative methods to assess determinants of implementation of our intervention and other guideline-based treatments for OSA and obesity, budget impact, and maintenance of patient-centered outcomes.

4. Findings/Progress to Date:
Recruitment began on 4/4/2022, analysis has not begun. No interim analysis planned.

5. Relevance to VA Mission
Our research tests a program of proactively providing Veterans with OSA the tools to manage weight loss in a way that is independent of local provider time and resources. Our research addresses a key gap in Veteran's health in a way that aligns with important VA priorities including population health, virtual care, access, and health care value. We anticipate our intervention can efficiently achieve improvements in quality of life while reducing the burden and risk of serious comorbidities.

List of Abbreviations

- Adverse event (AE)
- American Heart Association (AHA)
- Body mass index (BMI)
- Cardiovascular disease (CVD)
- Centers for Disease Control and Prevention (CDC)
- Centers for Medicare and Medicaid Services (CMS)
- Chronic obstructive Pulmonary Disease (COPD)
- Community based outpatient clinic (CBOC)
- Compensation & Pension Record Interchange (CAPRI)
- Computerized Patient Record System (CPRS)
- Confidence interval (CI)
- Continuous Positive Airway Pressure (CPAP)
- Corporate Data Warehouse (CDW)
- Data and Safety Monitoring Board (DSMB)
- Department of Defense (DoD)
- DVD Lifestyle Intervention (DELITE)
- Diabetes Prevention Program (DPP)
- Diabetes Prevention Support Center (DPSC)
- Digital video disc (DVD)
- Evaluation of Lifestyle Interventions to Treat Elevated Cardiometabolic Risk in Primary Care (E-LITE)
- Health Economics Resource Center (HERC)
- Health-related quality of life (HRQoL)
- Health Services Research & Development (HSR&D)
- Institute for Healthcare Improvement (IHI)
- International Physical Activity Questionnaire (IPAQ)
- Intra-class correlation (ICC)
- Institutional Review Board (IRB)
- Information Security Officer (ISO)
- Intention to treat analysis (ITT)
- Joint Legacy Viewer (JLV)
- Group lifestyle Balance (GLB)
- Managerial Cost Account (MCA)
- Medical Outcomes 12-item short form (SF-12)
- MOVE! Weight Management Program for Veterans (MOVE!)
- MyFitnessPal (MFP)
- National Archives and Records Administration (NARA)
- National Center for Health Promotion and Disease Prevention (NCP)
- National Institute of Health (NIH)
- Office of Information & Technology (OI&T)
- Obstructive Sleep Apnea (OSA)
- Patient-Reported Outcomes Measurement Information System (PROMIS
- Pragmatic Obstructive Sleep Apnea Weight Loss Trial Assessing Effectiveness and Reach (POWER)
- Pragmatic clinical trial (PCT)
- Primary care provider (PCP)
- Protected health information (PHI)

- Principal Investigator (PI)
- Randomized controlled trial (RCT)
- Record control schedule (RCS)
- Serious adverse event (SAE)
- United States Preventive Services Task Force (USPSTF)
- University of Pittsburgh (UP)
- Usual care (UC)
- VA Informatics and Computing Infrastructure (VINCI)
- VA integrated service network (VISN)
- VA Puget Sound Health Care System (VAPSHCS)
- Veterans Affairs (VA)

Contents

1.0 Study Personnel

Name/ Contact	**Role/ Affiliation**	**Access PHI**	**Recruit-ment**	**Surveys/ Interviews**	**Data Analysis**
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2.0 Introduction

2.1. BACKGROUND:

2.1.1. Obstructive sleep apnea (OSA) is a prevalent condition that poses a substantial burden to Veterans' health. OSA results in impaired respiration during sleep, leading to frequent oxygen desaturations and poor sleep quality.[1] OSA markedly reduces quality of life and is associated with serious comorbidities, including risk for cardiovascular disease that is up to 3 times greater than the general population.[1–4] Nearly 1.3 million Veterans are diagnosed with OSA, with prevalence rising two-fold in the last decade.[5] Faced with OSA's prevalence and associated morbidity, VA struggles to provide care that leads to meaningful improvements in health and wellbeing.[6]

2.1.2. Obesity is the primary driver of OSA, but VA's current approach to care exacerbates weight gain. Several population characteristics help explain Veterans' high prevalence of OSA such as advancing age and male gender, but by far the greatest contributor is obesity.[7] Excess weight explains a majority of OSA's incidence and severity,[7] and 75% of Veterans with OSA meet obesity criteria (~1 million Veterans). Despite the strong connection with obesity, VA's primary approach to OSA does not involve weight loss. Instead, VA's current strategy for OSA is to provide traditional first line disease management with positive airway pressure (PAP).[1,6] While PAP reduces airway obstruction and improves symptoms of OSA, it does not reverse its underlying cause. In fact, PAP worsens obesity, causing 0.5-2 kg in weight gain through reduced metabolic demands.[8,9] Furthermore, recent trials fail to demonstrate that PAP prevents cardiovascular events or improves metabolic disease (e.g. type 2 diabetes).[10–12] Clearly, additional strategies are needed beyond PAP to reverse OSA and its associated comorbidities.

2.1.3. Behavioral weight loss interventions show promise for OSA in carefully controlled efficacy trials, however important questions around real-world effectiveness remain. Lifestyle interventions targeting modest weight loss form the foundation of obesity management.[13] Accordingly, a number of efficacy trials studied the impact of behavioral interventions targeting dietary changes and exercise in OSA.[14] Participants randomized to weight loss in these trials achieved 5-7 kg in weight loss over 6-24 months and improvements in physiologic markers of OSA severity, with an average decline in apnea hypopnea index (AHI) of 8.3 events/hour.[14–16] Despite these promising results, recent clinical practice guidelines and state of the art reviews highlight a number of critical gaps in translating trial results into real-world impact.[14,17] One major gap concerns meaningful outcomes. Existing trials focused primarily on the efficacy of behavioral weight loss interventions to improve AHI, a diagnostic marker with often limited correlation with meaningful patient-centered outcomes (e.g. sleep-related quality of life).[18–22] While some secondary analyses suggest possible benefit, the evidence base is limited.[14] As a result, many question whether the benefits of modest weight loss in OSA are worth the expenditure of patient time, effort, and health system resources.[14] Critical questions also remain around how to integrate weight loss into usual care for OSA.[14] As we highlight below, such integration is lacking in VA.

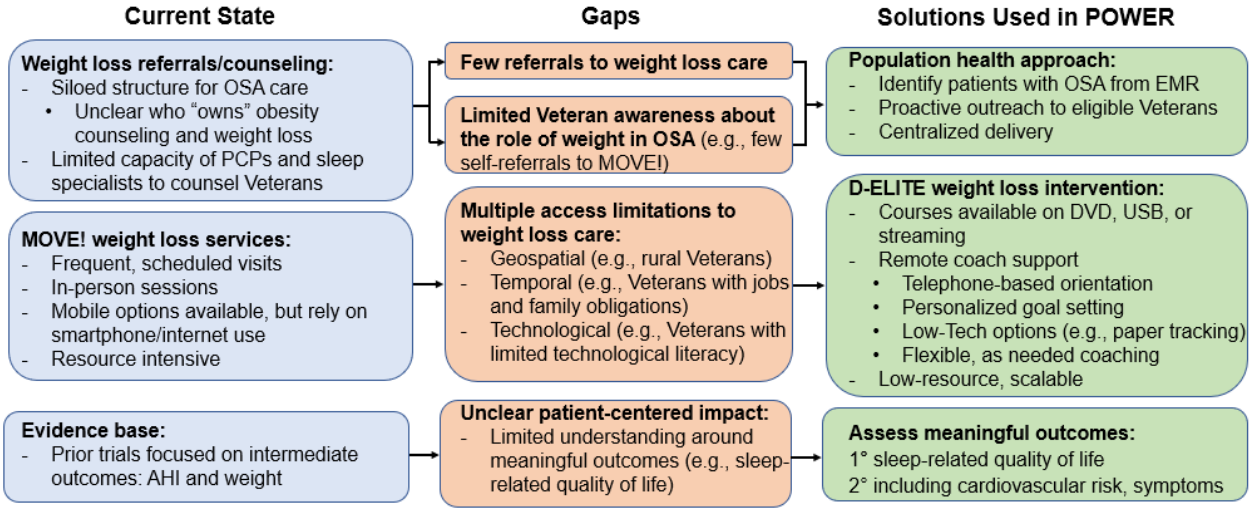
2.1.4. Existing structures in clinical care for OSA do not support weight loss counseling. Similar to patients with other conditions managed in specialty care, the management of patients with OSA is siloed.[23] Primary care providers are responsible for referring those with known or suspected of OSA, and sleep specialists provide diagnostic testing (e.g. polysomnography) and specialized disease management (e.g. PAP). In the current arrangement, there is no explicit understanding of who "owns" weight loss counseling. Furthermore, there is limited capacity in both groups for this task. VA has just ~300 sleep specialists nationwide to care for an OSA population of 1.3 million, limiting time for counseling and management of non-PAP care for

OSA.[24–26] Primary care providers face similar time-pressures that prevent discussions of weight loss.[27] As a result, fewer than 1/3 of Veterans with OSA discuss weight loss with providers, and Veterans rarely self-refer to VA's weight loss services (Section 2.5.2-3). Rather than rely on providers whose time is already constrained, weight loss interventions among patients with OSA could benefit from a population health approach that is independent of specialist or primary care providers. Improving access to lifestyle interventions has the potential to expand treatment for OSA and obesity.

2.1.5. VA's current weight loss offerings have poor accessibility, limiting overall effectiveness, particularly among patients with OSA. The behavioral weight loss interventions tested previously in OSA relied heavily on in-person sessions occurring at least once per week—intensity and structure replicated in VA's MOVE! program. While the intensive in-person model may work in clinical trial populations of highly motivated subjects, this format limits reach and effectiveness in the real world. In-person visits are a barrier for the 50% of Veterans who live >30 miles from the nearest facility, and scheduled sessions often conflict with Veterans' work and family obligations.[28,29] While telehealth options for MOVE! are available, up to 40% of enrolled Veterans do not regularly use the internet.[30,31] These barriers limit access, and our preliminary data suggest only 12% of Veterans with OSA and obesity engage with any MOVE! services (Section 2.5.2). Poor access also prevents continued attendance. Two-thirds of Veterans attend just 1-3 MOVE! visits leading to limited overall effectiveness.[31,32] For instance, Veterans with OSA in MOVE! lose just 1.2 kg at one year.[33] Recognizing the limitations of VA's offerings, the National Center for Health Promotion and Prevention (NCP) is interested in integrating new options to improve access, especially programs that are scalable, remote, and capable of reaching those with low tech literacy (See NCP Director Dr. Kim LOS). Disseminating accessible weight loss programs will be especially important in OSA. Patients with OSA often require greater engagement with behavioral weight loss programs in order to lose the same weight as peers without OSA,[33–35] reflecting the need to overcome PAP-related weight gain and metabolic effects of sleep disruption.[8,9]

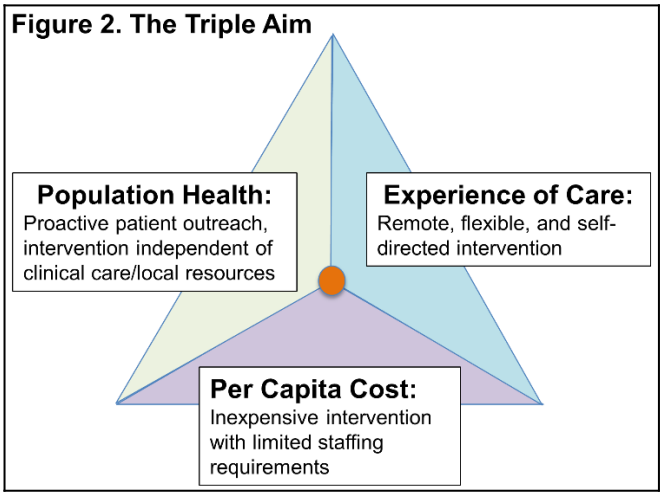
2.1.6. Summary of Background: Veterans with OSA comprise a large population where weight loss may offer substantial benefits to quality of life and reduce risks of morbid events. Despite promising results from efficacy trials of lifestyle-based weight loss programs, we have a limited understanding of weight loss' impact on meaningful outcomes and integration of weight loss into usual care. Veterans with OSA rarely receive weight loss counseling, and existing weight loss offerings have poor accessibility. Our research informs efforts to overcome these gaps using a novel population health approach (Figure 1).

Figure 1. Addressing Gaps in Weight Loss Care for Veterans with OSA



2.1.7. Framework: We designed this pragmatic trial, POWER, with the Triple Aim as our primary framework.[36] The Triple Aim provides a system-level model to optimize health system performance by simultaneously addressing three interdependent dimensions: patient experience of care, population health, and per capita health costs (Figure 2). **Experience of Care:** We propose a patient-centered approach to weight loss care among patients with OSA. Our remote intervention reduces geographic barriers and time required to travel and participate in appointments. The self-directed and remote nature of the intervention allows Veterans flexibility, enabling access for those with family and work obligations. **Population health:** Our intervention is independent of Veterans being seen in clinical care and uses administrative data to remotely identify and recruit patients, enabling centralized implementation. Unlike many other remote interventions, our intervention does not rely on Veterans having internet access or tech literacy, as course videos will be available by DVD and/or USB drive in addition to streaming. **Per capita cost:** The course videos for this intervention cost ~$16, and we will utilize a small number of staff to care for Veterans across multiple regions. We anticipate the intervention to be low-resource per capita. Finally, we acknowledge the Quadruple Aim and consideration of provider work-life.[37] Our population health approach addresses weight loss without additional demands on existing providers.

Figure 2. The Triple Aim



2.2. SIGNIFICANCE: Nearly 1 million Veterans have OSA with comorbid obesity, representing a population with markedly reduced quality of life at high risk for morbid resource-intensive conditions.[38,39] Although weight loss care has the potential to reverse OSA and other important comorbidities, such care is rarely offered, and when offered is frequently inaccessible. Providing scalable and accessible weight loss options is a high priority for NCP, and understanding how to integrate weight loss into usual care for patients with OSA is a key research priority for the field of sleep medicine (LOS from NCP and National Pulmonary, Critical Care, and Sleep Medicine,

NPCCSM, Program Director Dr. Yarbrough).[14] Our trial would address existing knowledge gaps in a way that is responsive to VA priorities including population health, virtual care, access to care, and health care value. **1) Population Health and Whole Health:** As outlined in the FY2018-24 strategic plan, a major priority of VA is to shift from a healthcare system focused on managing disease to one that supports Veterans in managing whole health and wellness.[40] Our research uses this approach for OSA care, empowering Veterans with tools to adopt healthy living strategies to improve OSA. Our strategies for patient identification and intervention deployment also facilitate a population health approach that is independent of provider referral or local resources. **2) Virtual Care:** Our lifestyle intervention, enables remote self-directed weight loss care using an evidence-based framework.[41] This lifestyle intervention further extends the reach of virtual weight loss care to those with low technology access, a key goal of NCP. Furthermore, the remote nature of our intervention enables deployment irrespective of social distancing measures for COVID-19. **3) Access to Care:** A chief goal of this research is to improve access to effective weight loss services, addressing gaps in VA's current weight loss offerings caused by geographic inaccessibility, busy schedules, and technological barriers. **4) Health Care Value:** By focusing on weight loss in OSA, our intervention efficiently targets quality of life in a way that may reduce risks for serious and resource intensive comorbidities (e.g., hypertension and cardiovascular disease). Our intervention aims to provide value to VA and Veterans by achieving meaningful improvements to population health at a small cost per-capita. We will rigorously assess the costs of the intervention and downstream utilization, and we will use these estimates to inform a budget impact analysis of widespread dissemination.

2.3. INNOVATION AND RESEARCH OVERLAP: Our study, POWER, is innovative in several ways.

Care Delivery Redesign: We directly challenge traditional models of healthcare delivery. Typical care is fundamentally provider-driven, relying on providers to direct care and provide services aimed at managing a single disease. While the provider-driven model is well suited for many conditions, this model is often inadequate for the promotion of healthy behaviors. Due to competing demands for provider time and attention, counseling for healthy behaviors and lifestyle change is often neglected.[24,27,42] POWER tests an alternative to this model by proactively offering and delivering weight loss services to a high-risk population.[3,13,14] **Remote and Self-Directed Weight Loss:** Obesity is a potent threat to both quality of life and health among patients with OSA, but weight loss services are often difficult to access.[14] POWER will be the first trial of self-directed weight loss among patients with OSA, addressing critical questions around effectiveness in a population where higher levels of engagement are often needed to achieve weight loss.[33–35] **Meaningful Outcomes:** Existing trials of lifestyle-based weight loss programs in OSA focused on their efficacy to improve AHI, an intermediate endpoint that often does not predict quality of life or other important patient-centered outcomes.[18–22] To approach this gap, we focus on sleep-related quality of life as a co-primary outcome and will prioritize additional secondary outcomes important to patients and policymakers (e.g. sleep symptoms and cardiovascular risk).[14] To further assess real-world effectiveness, we will use the RE-AIM framework to guide collection of implementation outcomes and estimates of public health impact.[43]Our group is in an ideal position to conduct this trial. We have experience in delivering the parent intervention, E-LITE, among patients with chronic obstructive pulmonary disease (NCT02634268). We also have an active trial deploying the current adaptation, D-ELITE, among Veterans in primary care (NCT03260140). These experiences provide us with expertise in delivering the intervention and collecting necessary outcomes (e.g., clinical, and self-collected weights). However, our ongoing trials do not inform critical knowledge gaps around a population health approach for high-risk patients or barriers and facilitators to widespread implementation. Furthermore, our existing trials do not inform meaningful outcomes among

patients with OSA, a large population for whom weight loss is difficult but may yield substantial benefits to health and wellbeing.

2.4. VETERAN ENGAGEMENT: To develop research that is consistent with Veterans' values, Dr. Donovan presented this project to the Seattle-Denver Center of Innovation Veterans Engagement Board. This eight-member board is composed of a diverse group of patients including members with OSA who had prior experience with the MOVE! program. The input of the board was instrumental in shaping our research. Based on their personal experiences with OSA and weight loss, Veterans on the board questioned whether weight loss by itself was a meaningful endpoint. Consistent with a patient-centered approach and known knowledge gaps (Section 2.1),[14] we are pursuing sleep-related quality of life as a primary endpoint, which the board felt to be more meaningful. Veterans also recommended additional considerations for improving access and broad-based engagement within the weight loss intervention. These include directing patients to existing resources to defray the costs of healthy eating and VA-based training for healthy cooking. The board also recommended that we promote flexibility around the types of physical activity that Veterans pursue. We will continue to work with the board as we pursue this intervention, and we will engage with Veteran participants within our process evaluation.

2.5. RESEARCH DESIGN AND METHODS:

2.5.1. Preliminary Studies: Our application draws on the strengths of our research team, fostering collaboration between VA and non-VA colleagues. Together, Drs. Donovan, Au, Ma, and Hoerster are recognized nationally as experts in sleep disorders, complex conditions, pragmatic trials, and weight loss interventions. We are ideally positioned to conduct this trial. Below, we describe the preliminary findings underlying this study's rationale as well as our group's experience in delivering the proposed intervention.

2.5.2. Veterans with OSA often do not discuss weight loss with providers and rarely engage with MOVE!: Supported by a VA Health Services Research and Development (HSR&D) Career Development Award and a multi-year grant from the Office of Veterans Access to Care, Dr. Donovan is conducting comprehensive evaluations of VA sleep care practices. In a representative cohort of 4,030 Veterans with obesity and OSA referred to sleep medicine from May 2018 to May 2019, only 12.2% had one or more MOVE! or nutrition visits in the year after referral. Highlighting geographic barriers, every 20 minutes of drive time were associated with 0.85 odds (95% CI 0.74-0.96) of MOVE! utilization. Furthermore, weight loss in general was infrequently addressed. In surveys of randomly selected patients with OSA, only 32.7% of Veterans recall discussing weight loss with providers relative to 82.7% who recall in-depth counseling for PAP therapy.

2.5.3. Among Veterans with OSA referred to MOVE!, weight loss is minimal: In collaboration with other VA researchers, Dr. Hoerster analyzed nationwide administrative data to assess weight loss among patients referred to MOVE!. Veterans with a diagnosis of OSA lost 1.1kg (95% CI 1.0-1.2) at 6 months and 1.2 kg (95% CI 1.1-1.3) at one year. Consistent with findings outside of VA, Veterans needed greater engagement with MOVE! in order to lose similar amounts of weight as peers without OSA.[33–35]

Together with information outlined in the background, and with concurrence of NCP, our findings reinforce the need for new weight loss options among patients with OSA that are accessible and effective.

Table 1. Video session topics

1. Getting Started Losing Weight
2. Be an Excess-Calorie Detective
3. Healthy Eating
4. Move Those Muscles
5. Tip the Calorie Balance
6. Take Charge
7. Problem Solving
8. Four Keys to Healthy Eating Out
9. Slippery Slope of Lifestyle Change
10. Jump Start Your Activity Plan
11. Make Social Cues Work for You
12. Ways to Stay Motivated

2.5.4. Proven successful adaptation of the highly effective DPP weight loss intervention into a remote self-directed intervention: The landmark DPP trial demonstrated that an intensive lifestyle intervention targeting modest weight loss and increased physical activity markedly lowered type 2 diabetes incidence in diverse populations, with effects persisting up to 10 years.[44] Despite the benefits of DPP on diabetes risk, the highly intensive intervention did not readily lend itself to implementation. DPP investigators adapted the resource intensive, primarily one-on-one lifestyle intervention to a group program with fewer sessions called Group Lifestyle Balance (GLB).[45] The program is effective for weight and cardiometabolic risk reduction, implemented using existing staff (e.g. dietitians, lay health educators) in varied settings (e.g. primary care, medically under-served, rural).[45,46]

Expanding on this work, Dr. Jun Ma adapted DPP and GLB to implement E-LITE (Table 1). The E-LITE self-directed intervention consisted of a single group orientation, after which patients received take-home DVDs (now available online and on USB drives) based on the GLB curriculum with twelve 25-minute weekly sessions and associated handouts (Table 1). Content focused on healthy diets, physical activity, and behavior change. These video sessions were supplemented by self-monitoring of weight and physical activity, and access to a trained lifestyle coach. Participants accessed a free and secure online portal for self-tracking (e.g., weight and activity), messaging between participant and coach, and automated reminders. In Dr. Ma's randomized trial of 241 patients, both the self-directed E-LITE lifestyle intervention and an intensive coach-led group intervention produced comparable clinically significant weight loss over 2 years among adults at risk for diabetes (Figure 3). This finding is important as weight loss trends at 2 years are strong predictors of sustained weight loss.[47,48]

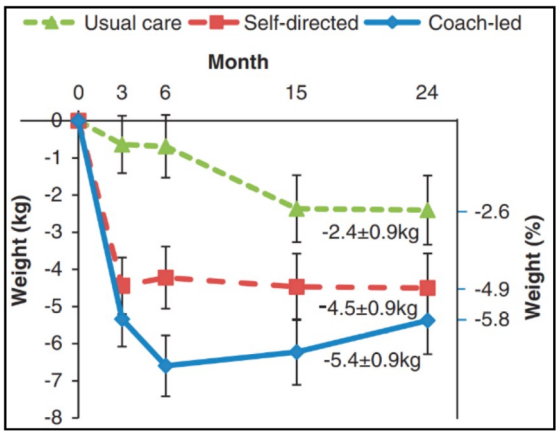


Figure 3: Mean ± SE weight change in E-LITE

Table 2. Evolution of weight loss intervention programs and trials that resulted in the current trial

Study/Program	Brief Description
DPP Trial	Multicenter efficacy trial showing superiority of DPP lifestyle intervention to metformin and placebo.
GLB Program	Direct adaptation of the DPP lifestyle intervention, recognized by the CDC National DPP initiative, disseminated through the University of Pittsburgh Diabetes Prevention Support Center (DPSC).
E-LITE Study	Randomized trial in primary care integrating the GLB core curriculum with online monitoring. Compared delivery in-person or by take-home DVD to usual care. Results: The two GLB delivery modes showed comparable efficacy vs. usual care among privately insured patients.
POWER Study	Pragmatic type I hybrid effectiveness-implementation trial of E-LITE with low-technology adaptations (D-ELITE) delivered proactively to Veterans with OSA and obesity.

To improve the E-LITE self-directed intervention for ease of Veteran participation, D-ELITE replaces the single group-orientation visit with a one-time telephone-based orientation. This orientation includes an overview of diet and exercise strategies. D-ELITE offers Veterans options for how to engage with the intervention subsequently: DVD, USB, or online access to the same 12-session videos, self-monitoring using paper booklets or a free web-based tracker (MyFitnessPal), and coach access by phone. Prior work indicates that the method of self-tracking is less important than the self-tracking behavior itself.[49] Telephone based lifestyle coaching is recommended in the latest obesity treatment guideline.[50] Together, these options improve flexibility of delivery and engagement for Veterans who do not use technology. Collectively, the D-ELITE intervention has been adapted from a highly efficacious, but limited reach intervention to one that is less burdensome to patients and VA (Tables 2,3).

Table 3. Original E-LITE self-directed and current intervention components summary

E-LITE Self-Directed	D-ELITE in the POWER study
One-time group-based in-person orientation	**One-time one-on-one telephone** orientation.
Take-home DVDs with participant handouts for 12 weekly sessions. (~25 min ea.)	**Mailed** USBs and/or DVDs with participant handouts for 12 weekly weight loss sessions. (~25 min ea.)
Recommended daily **self-monitoring of weight and physical activity online**; patients entered weights and minutes of physical activity	Recommended daily **self-monitoring of weight, physical activity online OR via paper tracker**; patients entered weights and minutes of physical activity
Access to a trained lifestyle coach for questions and counseling, at patient request, **via online secure messaging**	Access to a trained lifestyle coach for questions and counseling, at patient request, **via secure messaging or telephone**

2.5.5. Expertise in identifying and recruiting patients for pragmatic clinical trials: Drs. Donovan and Au have focused their research on improving delivery of care for patients with complex chronic conditions, including OSA. The success of this pragmatic trial relies on using existing resources and infrastructure to support clinical trial activities. Dr. Donovan has developed substantial experience in utilizing VA data structures to assess sleep related predictors and outcomes, including nationwide assessments of

Table 4. Weight Δ measured in clinic or by researchers

Trials	N	Clinic (slope)	Research (slope)	Slope difference (95% CI)
E-LITE				
Self-directed	81	-0.05	-0.11	0.06 (-0.03, 0.15)
Coach-led	79	-0.11	-0.12	0.01 (-0.07, 0.08)
Control	81	0.00	0.01	-0.01 (-0.09,0.06)
BE WELL				
Coach-led	165	-0.02	-0.04	0.02 (-0.01, 0.06)
Control	165	0.00	-0.02	0.02 (-0.02, 0.06)

Table 4. Weight Δ measured in clinic or by researchers

Trials	N	Clinic (slope)	Research (slope)	Slope difference (95% CI)
E-LITE				
Self-directed	81	-0.05	-0.11	0.06 (-0.03, 0.15)
Coach-led	79	-0.11	-0.12	0.01 (-0.07, 0.08)
Control	81	0.00	0.01	-0.01 (-0.09,0.06)
BE WELL				
Coach-led	165	-0.02	-0.04	0.02 (-0.01, 0.06)
Control	165	0.00	-0.02	0.02 (-0.02, 0.06)

sleep study utilization.[51] Dr. Au has a wealth of experience in using the Corporate Data Warehouse (CDW) to recruit for large clinical trials, including two adaptations of the E-LITE intervention (NCT02634268; NCT03260140).

2.5.6. Using clinical versus research weights. Our approach in this trial will rely on clinically measured weights to assess one of our primary outcomes. To assess the validity of such an approach, we compared differences between research and clinically measured weights in two weight loss trials, E-LITE and BE WELL.[52] In these trials, the slopes of weight change did not differ if clinic or researcher measured weights were used (Table 4). Furthermore, no difference in trial interpretation occurred when using clinic or research measured weights, supporting the use of clinical weights in pragmatic trials.[52]

2.5.7. Availability of vital signs in CDW and feasibility of self-collected weights. Based on the validity of clinic relative to research weights, we pursued clinical weights as our primary outcome in a prior VA weight loss trial (NCT03260140). In this trial, 84% of participants had a repeat outpatient clinic-derived weight and blood pressure measurement within 3 months of a 12-month follow-up. In a subset, we also asked participants to weigh themselves using study supplied scale in a manner approximating clinic weights (e.g., clothed with no shoes or jacket). These self-weights strongly correlate with clinic weights (r=0.94). Our methods in capturing self-reported weights achieved <5% missingness across our sample.

3.0 Objectives

In POWER, we propose a pragmatic hybrid type I randomized control trial of adding the lifestyle intervention to usual care for Veterans with OSA and obesity. We will take a population health approach by proactively offering weight loss and delivering the lifestyle intervention independent of provider referral or resources. Our primary focus is effectiveness for meaningful outcomes, and we will also assess determinants of widespread implementation of our intervention, alternative guideline-based treatments for OSA and obesity, and the achievement of patient-centered outcomes.[43]

Primary Aim: Test the effectiveness of a proactively delivered and pragmatic weight loss intervention to improve sleep-related quality of life and weight among patients with OSA and obesity.

Secondary Outcomes and Measures:

1. Additional effectiveness outcomes including changes in sleep symptoms, cardiovascular risk scores, blood pressure, and physiologic OSA severity (AHI)

2. Implementation outcomes informed by the RE-AIM framework including Reach, Adoption, Implementation (including costs/budget impact analysis), and Maintenance

Hypotheses:

H1 (Primary Hypothesis): Lifestyle intervention will lead to greater weight loss and improvement in sleep-related quality of life at 12 months relative to usual care.

H2a (Secondary Hypothesis): Lifestyle intervention will lead to greater improvement in secondary outcomes relative to usual care.

H2b (Secondary Hypothesis): Self-directed lifestyle intervention will lead to lower 12-month AHI relative to usual care.

4.0 Resources and Personnel

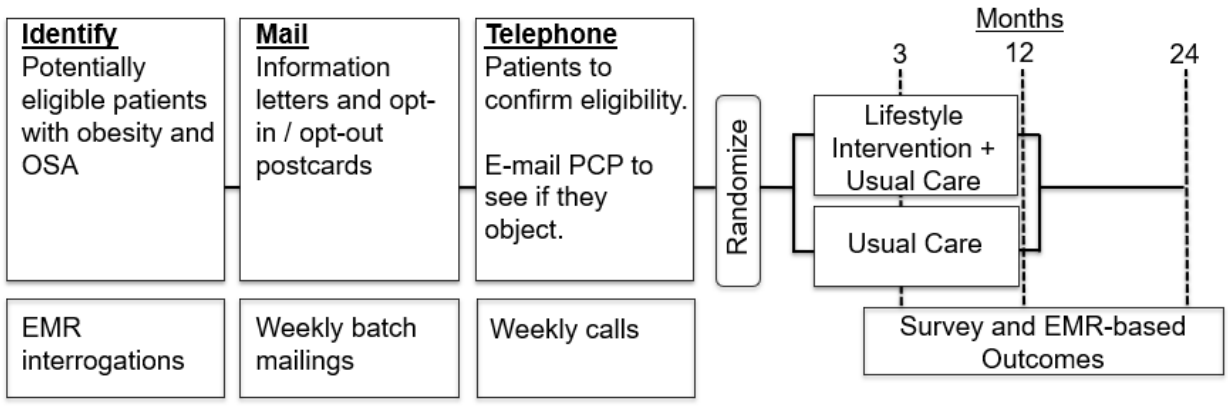
All study personnel are listed in Section 1.0, including their contact information. Also detailed in that section: affiliation, role in study, who will have access to protected health information, who will be recruiting, consenting, administering surveys and who will perform data analysis.

5.0 Study Procedures

5.1 Study Design

5.1.1. Proposed study design: POWER is a type 1 hybrid pragmatic RCT in which 696 Veterans with OSA and obesity will be randomized to usual care or usual care enhanced with the D-ELITE self-directed lifestyle intervention for 12 months. Our primary outcomes are change in sleep-related quality of life and weight at 12 months (Figure 4). We will assess secondary outcomes at 3, 12 and 21 months.

Figure 4.



We are also conducting an implementation process evaluation as described in 5.5.7.

5.2 Recruitment Methods

5.2.1 Enroll Veterans nationwide with OSA and obesity

5.2.2 Identify eligible participants through CDW:

We apply CDW algorithms to identify potentially eligible participants and verify eligibility via chart review using approved platforms including JLV/CAPRI (see Table 4, Section 5.4).

5.2.3 Screening for index weight/BMI:

Using CDW, we will identify Veterans with prior sleep study (CPT 95800, 95801, 95806, 95810, 95811), with associated diagnosis of OSA, an eligible BMI (index weight), a weight measurement indicating obesity (to minimize spurious inclusion), and who are likely free of exclusionary conditions searchable in CDW. We will retain pertinent socio-economic, demographic, and healthcare utilization data on all individuals identified to inform our organizational partners about the potential reach of the program.

5.2.4 Oversampling:

We may oversample:

- Women – our goal is to enroll approximately 30% of the cohort being female;
    - As we approached a third of our randomization goal, we observed that approximately 25% of enrollees were female. In order to increase our target oversampling, we may evaluate and re-mail an invitation to women. Our criteria include female non-responders who had an initial mailing at least 2 weeks prior and have an end of window greater than 2 weeks away.
- Minorities, if necessary, to have a balanced proportion of the cohort

5.2.5 Research invitation:

Using patients identified through CDW, we will mail and/or email invitations to enough Veterans to enroll 696 subjects. The invitation will contain:

- Flyer;
- Invitation Letter;
- Information Sheet;
- Opt in/out Post Card;
- Email decryption instructions;

We may pursue the option of posting the packet on the HSR&D public website for easy access in the future.

In order to meet our target recruitment timeline, we may re-mail and/or re-email to non-responders if they have not replied two weeks or more after initial mailing/emailing.

Once we meet our randomization goal, we will inform participants who have opted-in but are not yet randomized that enrollment is closed.

5.2.6 Recruitment of Lifestyle Coaches for Interviews. Lifestyle coaches will be research study staff who will complete the Group Lifestyle Balance Training (described in 5.3.5.3). To inform wider dissemination, we plan to assess staff experiences with the lifestyle coaching intervention. We will therefore perform qualitative focus group discussions among study staff members who are working in the lifestyle coaching role.

During this study, the qualitative Co-I on the team will contact each lifestyle coach by email to invite them to participate in a focus group discussion during year 2 of the project. The qualitative Co-I will not be the supervisor of any lifestyle coach that he or she invites.

The qualitative Co-I will schedule and perform the focus group discussion with verbal informed consent under a waiver of documentation of informed written consent. Note: The focus group discussion is not planned to occur until year 2 of the project. We may submit a modification with the email and edits to the interview guide.

5.3 Informed Consent and Randomization

5.3.1 Telephone screen, consent, and baseline assessment:

For those potential participants who do not return an opt-out postcard within 2 weeks (as well as those who return the opt/in card and those that opted in via Qualtrics), a research coordinator may telephone to:

- Describe study and answer questions.
- Assess eligibility, including potential exclusions for safety. (Section 5.4)
- Obtain consent under a waiver of documentation of written informed consent.
- Administer baseline surveys; or participant may complete online versions or paper copies and return via postage-paid mail.

5.3.2 Medical clearance:

For individuals who consent at the telephone screen and have fulfilled safety requirements, study staff will send a secure email to the patient's primary care provider to inform them of their patient's participation and to alert us if there is any reason that their patient should not participate. If the primary care provider does not respond after four days, we will send a second email. If no response to the second email, we will send a third email informing the PCP that we will enroll the individual in three business days unless they contact us otherwise. We will inform interested participants if their provider responded that this intervention is not appropriate.

As outlined in section 5.5.6, a subset of POWER subjects will be selected to have a single-night diagnostic home sleep study at 1 year. Among those selected for this sleep study, study staff will send a secure email to the patient's primary care provider and, if available, their sleep specialist. This email serves to inform their providers of their patient's participation in a single-night sleep study, asks if they have any concerns about their patients' participation in this diagnostic sleep study, and states that we will proceed with the sleep study unless the specialist contacts us within five business days. As diagnostic sleep studies, proposed in this trial, are often used as part of usual care to diagnose OSA and observe changes in patients' OSA severity over time, we do not expect that many providers will object to participation.

5.3.3 Randomization:

POWER staff will randomize each participant into the usual care or intervention group at a ratio of 1:1. Participants must have PCP clearance and completed baseline surveys before randomization can occur. Randomization should occur no more than sixteen weeks after the date of the index weight. After sixteen weeks we may ask the participant to return to the primary care clinic for a new index weight if still not randomized. We will notify participants of their randomization group via mail and/or email. The mailing will include a weight scale for all participants and the additional materials (DVDs and/or USB drives, instructional handouts, GLB curriculum, Calorie King Fat & Carbohydrate Counter, and paper tracking booklets) for intervention participants.

5.3.4 Stratification: Given three stratifying variables of BMI category (strata: 30-34.9 vs. 35-44.9 kg/m2), physiologic OSA severity (moderate to severe as defined by interpreting physician or apnea hypopnea index ≥15 events/hour vs. otherwise) and sleep related impairment (PROMIS Sleep Impairment T-score ≥ 60 vs. T-score <60) there will be 8 strata. Stratification may help prevent covariate imbalance between groups.

5.3.5 Continuation of usual care: We will provide all control patients with the same weight scale as we provide to intervention patients. All participants will continue to receive standard care for OSA from their usual primary care and sleep providers. We chose usual care only for our control group because pragmatic RCTs are most useful in testing interventions in real-world settings and addressing the question “how does the intervention compare to what we are doing now?” We believe that including an alternate approach such as an attention control condition would undermine the purpose of this trial. Our study will not interfere with ongoing patient care, including referral to MOVE!, PAP prescriptions, or other sleep treatments. To protect external validity, no participant will be instructed not to seek weight loss or OSA treatment. We will include all participants in the intent to treat analysis. We will monitor electronic health record (EHR) data for participation in MOVE! and patient report for participation in non-VA weight loss programs. We will monitor PAP use through VA approved manufacturer-specific portals (Phillips Encore, ResMed AirView) as well as VA approved data management systems (e.g. Somnoware).[53]

5.3.6. Intervention and its theoretical basis: Like its predecessors, POWER will use the GLB lifestyle intervention which is grounded in Social Cognitive Theory (SCT),[54] and uses self-regulation strategies (goal setting, self-monitoring, planning, and problem-solving) to achieve and maintain realistic intervention goals: losing 5-10% of baseline weight and participating in ≥ 150 minutes/week of moderate-intensity physical activity. SCT emphasizes reinforcing relationships between the individual, environment, and behavior, recognizing that self-efficacy is enhanced through social support and gradual mastery of self-regulation. Further, SCT builds on an assumption that long-term changes in behavior are most likely to occur when the strategies used to motivate and support behavior change are flexible, sensitive to individual differences, and broadly acceptable to those in the target population. The GLB video program provides specific instruction in these goals for diet and weight loss (Section 2.5.3).

5.3.6.1 Evidence-based goals: Weight: The intervention is designed to achieve and maintain gradual weight loss of 5-10% of baseline body weight. This amount of weight loss is safe and feasible.[41,44] To achieve and maintain weight loss, we will advise participants to reduce their calorie intake by 500-1000 kcal/day, as recommended in adult obesity guidelines, including OSA

specific guidelines and the VA DoD clinical practice guideline.[13,14,50] Participants will gradually achieve calorie goals through portion control, low-energy, and nutrient-dense foods (e.g. fruit, vegetables, whole grains, non-sweetened dairy products), reduced consumption of refined carbohydrates/sugars, healthy food preparation techniques, and careful selection of restaurant items. Physical activity: The physical activity goal is to achieve and maintain a minimum of 150 minutes per week of moderate-intensity physical activity (e.g., brisk walking). This goal is consistent with the Physical Activity Guidelines for Americans,[55] and is safe and attainable for most adults including those with chronic health conditions. Participants will gradually and steadily increase daily walking with a goal of achieving 150 minutes of brisk walking per week by the end of the 12-week video program (Table 1). Participants may also choose to adopt regular activities of moderate intensity other than brisk walking,[56] and we will encourage referrals to local rehabilitation services for individuals with addressable mobility limitations.

5.3.6.2. Format, Structure, and Content: There is a national call for providing multicomponent lifestyle interventions for obesity and integrating this care into OSA management.[14,50,57] The challenge with such interventions is that they are difficult to deploy in the real world. The Center for Medicare and Medicaid Services reimbursement policy promotes brief (15 minute), lower intensity, face-to-face behavior counseling within a limited timeframe (6-12 months).[14,50,57] Our intervention fits this general pragmatic framework within a self-directed approach using remote delivery and low staffing requirements. This study is intended to contribute to the evidence base needed to inform and further guide policy change, in the context of growing interest and evidence in effective and pragmatic interventions for OSA.

Immediately after randomization, the study staff will mail a weight scale to all participants and the additional materials (DVDs and/or USB drives, instructional handouts, GLB curriculum, Calorie King Fat & Carbohydrate Counter, and paper tracking booklets) to intervention participants. Coaches will then call participants to confirm package receipt, review materials and instructions, confirm understanding, and address any questions. Similar to the E-LITE self-directed intervention, we will deliver the intervention's core curriculum in the first 3 months using the 12-session GLB videos available via DVD, USB drive, or online streaming per Veteran preference. Veterans will also be able to choose to engage in self-monitoring of weight and activity using a web-based program (MyFitnessPal) or paper GLB booklets. A lifestyle coach will reach out every other week with messages through MyFitnessPal or text message reminding participants to watch the designated GLB video session and continue self-monitoring. We will instruct participants to contact the lifestyle coaches via MyFitnessPal messaging or phone if they have questions or would like behavioral counseling. Participants are asked to watch one ~25-minute video session a week. As recommended by guidelines, the main objective of the core curriculum (months 1-3) is to facilitate gradual weight loss through successive and progressive changes in diet and physical activity and behavioral skills training. Months 4-12 focus on continued self-directed/monitored gradual weight loss and maintenance. Participants will have access to the lifestyle coach for all 12 months of the intervention.

Self-monitoring is key to successful behavioral weight-loss interventions.[58] E-LITE results support a positive relationship between frequency of self-monitoring and weight loss.[59] We will encourage participants to continue self-monitoring through MyFitnessPal or paper trackers beyond the 3-month core intervention. The coaches will set up email reminders and text message alerts through MyFitnessPal or possibly ANNIE (does not require a smart phone).

In prior deployments of E-LITE, patients required an initial 1-hour orientation, biweekly templated messages (2 minutes/message), and ad-hoc counseling sessions 2 times per month (7 minutes/session). Based on these estimates, a 1-FTE coach could conservatively manage 450 patients over the course of a year. This centralized, off-site staffing approach is not only

necessary for this protocol to be feasible (as opposed to identifying and training lifestyle coaches at the participants' clinical centers) but also enhances practicality for regional implementation. The DPP training session, previously through the University of Pittsburgh, now conducted by SPARK Pro training, will train lifestyle coaches in diet and exercise counseling, with virtual options available given COVID-19 pandemic.

5.3.6.3. Lifestyle Coach selection and training: The lifestyle coaches will be study staff employed by VA Puget Sound as part of the research team. Each lifestyle coach will receive formal training from the University of Pittsburgh's Group Lifestyle Balance Virtual Training Workshop now through SPARK Pro (http://sparkprotraining.com/).

5.3.6.4. Adherence: As in E-LITE, POWER will not use special strategies to maintain or improve adherence to the intervention. Through MyFitnessPal messages or possibly ANNIE texting, participants will be periodically prompted to view the weekly session video and continue self-monitoring. We will assess adherence in 3 ways. 1) Self-monitoring among Veterans using MyFitnessPal (83% of participants in prior trials of E-LITE) will be downloadable to the team. Remaining Veterans will use study-provided paper-based self-tracking booklets, which will be mailed back to study staff. 2) Number of sessions and handouts viewed will be tracked by engagement surveys sent at 3m and 12m post randomization. 3) We will record the number and indication for contact with lifestyle coaches. These assessments will allow us to explore relationships between adherence and outcomes in post-hoc analyses.

5.3.7. Participant compensation: Participants completing 12-month outcome surveys will receive $25. At the end of the 12-month period, participants that have completed the lifestyle intervention interview and/or the sleep study will be compensated for their participation with a $25 payment for either. At the end of the 21-month follow up outcomes data collection window, participants that completed any of the questionnaires will be compensated for their participation with a $25 payment. Participants will also be allowed to keep the body weight scale used during the study. Participant payments may be in the form of check, direct deposit or gift card.

5.4 Inclusion/Exclusion Criteria

Veteran Participant eligibility criteria: As we describe in more detail below, we will utilize the CDW to identify Veterans with recent sleep study and diagnosis of OSA with measured body mass index (BMI) between 30.0-44.9 kg/m^2 recorded in the past three months. Including patients with recent sleep study will increase likelihood of accurately identifying participants with OSA,[60] and will allow recruitment after initial diagnosis or reassessment when patients may be more amenable to behavior change interventions.[61]

To minimize spurious inclusion, we will ensure an additional BMI within the past 12 months of index weight that meets criteria set by a standard algorithm to remove implausible and erroneous BMI values.[29,62,63] Specifically, we use the criteria used previously for the D-ELITE trial[62,63] to exclude any index weight indicating excessive weight change prior to the index date: >40-pound change in any 30-day period in past year, or more than two pounds change per week over periods greater than 30 days. To exclude plausible but likely invalid index weights, we excluded weights if 1) the standard deviation of the difference between index and any past-year weight is greater than 5% of the average weight, 2) if the weight change is greater than ±100 pounds in a year, or 3) if the BMI change is greater than ± 15 kg/m^2. We also exclude weights greater than 500 pounds or less than 90, height < 49 or > 84 in., and BMI greater than 65 or less than 15 kg/m^2 (calculated using the most recent height measurement between 49 and 84 in.). We apply the same algorithms for flagging potentially implausible and erroneous weights for outcome measurement (Section 5.5.2).

We will also confirm OSA by reviewing sleep studies, among those who have not opted out, prior to enrollment. We will calculate index and previous BMI using most recent height and weight. Exclusion criteria are chosen to ensure participant safety, while maximizing internal validity, and minimizing error caused by missing and misclassified data (Table 4).

Table 4: Inclusion and Exclusion Criteria

Inclusion

- Diagnosis of OSA on sleep study (sleep provider confirmed)
- Clinical BMI between ≥ 30, < 45 kg/m^2, and at least one additional plausible BMI in last 12 months
- Access to television and DVD player, computer with USB drive, or internet
- Able to participate fully in all study protocol/procedures including informed consent

Exclusion

- Inability to speak, read, or understand English
- Recent or active weight loss interventions including prescription weight-loss medications in last 90 days, participation in group or individual weight loss programs led by trained personnel in the past 90 days, and prior bariatric surgery or plans for bariatric surgery during the study period.
- Expected weight loss because of alternate explanations such as from illness
- High variability in weight due to fluctuations in volume status (e.g., ascites - liver disease, chronic heart failure)
- Safety and/or adherence concerns due to severe physical or mental health issues or life expectancy < 24 months. For example:
    - 1) Outpatient health encounter within the last year for malignancy, chronic respiratory failure, schizophrenia, psychosis, dementia, substance use disorders, anorexia, bulimia, binge eating disorder
    - 2) Hospitalization in the last 6 months
    - 3) Receiving hospice or palliative care.
- Pregnant or planning to become pregnant during the study period
- Participation in other intervention studies

Phone Screening prior to randomization: To further ensure identification of exclusions (Table 4), study staff conduct a brief phone screening questionnaire during recruitment. Included in this screening, as of February 2023, will be a series of questions aimed at identification of eating disorders. Should a potential eating disorder be identified, the Veteran will not be enrolled in the study.

Non-Veteran Eligibility Criteria: As described in 5.2.6. We will approach all study staff employed as lifestyle coaches for qualitative interviews.

5.5 Study Evaluations

5.5.1 Baseline and follow-up effectiveness measures and data collection: Table 5 shows the study measures and data collection schedule. We have extensive experience with the requirements for administering all the measures proposed. Research coordinators may administer baseline and 3, 12, and 21-month follow-up surveys via telephone, record responses

on paper, or Qualtrics, and enter values into study databases using double data entry and logic controls to minimize error. To emulate paper surveys and study staff calling after review, Qualtrics will prompt participants to respond to questions if they accidently left them blank. Furthermore, personalized survey completion messages will be incorporated into Qualtrics to direct participants to the next action. Other slight modifications (e.g., bolded fonts, transition pages, and sub-headers) of Qualtrics can be accounted by the formatting appeal of the online interface. We will assess information using a health inventory checklist including socio-demographic characteristics, health behaviors, global impression of change, and non-VA weight loss programs. We will obtain additional information about comorbid conditions, medication use, healthcare utilization, and distance to clinics from the CDW. We will compensate participants $25 if they complete the 12-month packet in the follow-up window and an additional $25 at the end of 21-month follow-up period if they completed 3,12 (if not already compensated), or 21-month outcome surveys.

Table 5: Measures and timing of collection

Variable	Source	B	3m	12m	21-24m
Baseline variables and covariates					
Height	EMR	X			
Clinical AHI	Chart review (JLV, CAPRI)	X			
Demographics	Self-report	X			
Non-VA weight loss program	Self-report	X	X	X	X
Adherence to Intervention	Survey		X	X	
Outcomes					
Primary Effectiveness Outcomes					
Sleep-related quality of life (FOSQ)	Surveys	X		X	
Weight (clinical)	CDW	X		X	
Secondary Effectiveness Outcomes					
Cardiovascular Risk Score	CDW	X		X	X
Weight (Clinical)	CDW	X	X		X
Weight (Self-report)*	Survey		X	X	X
FOSQ	Survey	X	X		X
Blood Pressure	CDW	X		X	X
Global Impression of Change	Survey		X	X	X
Sleep Symptoms	Survey	X	X	X	X
Well-Being	Survey	X	X	X	X
Objective PAP adherence	Remote Downloads	X	X	X	X
Self-reported adherence to sleep apnea treatments	Survey	X	X	X	X
Sleep Duration	Survey	X	X	X	X

Research AHI**	HSAT			X	
*-Collected as needed as a contingency outcome if no clinical weights. Also collected shortly after randomization following receipt of trial scale **-Outcome only collected among a subset of up to 250 participants					

5.5.2. Primary Outcomes: The co-primary endpoints for our pragmatic trial are changes in sleep-related quality of life and weight from baseline to 12 months. In secondary analyses, we will assess these outcomes at additional timepoints. Sleep-Related Quality of Life: The functional outcomes of sleep questionnaire (FOSQ) assesses multiple activities of daily living impacted by sleep disorders.[64] FOSQ addresses domains that are important to patients: activity level, vigilance, intimacy/sexual relationships, productivity, and social outcome. FOSQ has a high degree of internal reliability, strong criterion, and construct validity when compared against generic quality of life measures (e.g. SF-36) and sleep symptom inventories.[65] FOSQ is sensitive to changes in OSA treatment and is widely used in trials of OSA management. Weight Loss: Consistent with the pragmatic nature of this trial, we will prioritize clinically measured weights using methods shown to be feasible and valid when compared to research weights (Section 2.5.6). We will use participants' qualifying outpatient clinical weight in the four months prior to randomization as their baseline measure. To assess change, we will select the outpatient clinical weight that is closest to the 12-month post-randomization date within a 9–15-month post-randomization window, using a standard algorithm to remove implausible and erroneous values.[29,62] Specifically, prior to unblinding, suspect weights will be flagged using criteria used in the D-ELITE trial.[62,63] These criteria are the same as those used above for exclusion in the baseline period. Flagged weights will be reviewed in a blinded fashion by study staff for plausibility. Weights determined to be implausible or likely erroneous will be excluded from analysis. As in D-ELITE, we will prioritize primary care clinic weights, however we will substitute another outpatient clinic weight from within our collection window if a primary care weight is missing. To reduce missingness, we will ask patients to schedule a visit with their primary care clinic for a weight if they do not have a clinical weight documented by 12-months. We have found that patients can have vital signs checked and entered into the EMR without an encounter or co-pay. We used these methods in a prior VA weight loss trial and obtained follow-up clinic weights in 84% of participants (NCT 03260140).

Contingency for weight:
We fully acknowledge that ongoing COVID-19 related changes in clinic utilization may alter the feasibility of the clinic-based approach. As a contingency, we may also request that participants weigh themselves with study-provided scales and report measured weights shortly after randomization as well as at 3, 12, and 21-month follow-up. If weights are reported via Qualtrics, we have incorporated a validation response to imitate paper survey values. Under a contingency approach that we will explore in secondary/sensitivity analyses, if a subject is missing a clinical weight, we may substitute the self-collected weights for baseline and/or follow-up values in the analysis. We will provide written and verbal instructions to approximate clinic-based weights (e.g., clothed, but no shoes or jackets). Should we experience widespread closures, limiting assessments of clinical weights, we may consider substituting clinical weights with self-weights in our primary analysis. We would make such a decision prior to analyzing primary outcomes.

5.5.3 Secondary Effectiveness Outcomes: We will assess additional secondary outcomes meant to gain a more complete understanding of the intervention's impact. Consistent with the pragmatic nature of our trial, we prioritize outcomes that can be obtained from the electronic medical record, reducing participant burden.

Secondary Effectiveness Outcomes Collected in General Clinical Care: Cardiovascular Risk Scores: We will use CDW data to calculate a cardiovascular risk score designed by the Framingham Heart Study,[66,67] which incorporates age, BMI, systolic blood pressure, antihypertensive medication use, current smoking, and diagnosis of diabetes. The non-laboratory risk score replaces lipid values with BMI and is comparable to the standard Framingham Risk score in predicting cardiovascular events.[67] The non-laboratory Framingham score is particularly well-suited to pragmatic trials using data collected in usual care, and is responsive to weight loss interventions.[68] Our group has extensive experience in obtaining each of the required data elements from CDW.[51] We will also supplement collection of information about current antihypertensive use, smoking, and diabetes status with participant self-report on baseline and 3 , 12, and 21 month follow-up surveys. Blood pressure: We will obtain diastolic and systolic values from the CDW. Based on prior work in an ongoing trial, we anticipate >80% of subjects will have clinical follow-up measures (Section 2.5). PAP Adherence: We will explore the impact of weight loss on PAP usage and will assess PAP use as a mediator in secondary analyses of the intervention's impact on primary and secondary outcomes.[14] All PAP machines dispensed by VA transmit adherence, with results accessible in routine care through secure platforms.[69,70] We will collect 90-day PAP adherence at 3, 12 and 21 months. We also collect self-reported adherence to PAP and other treatments at 3, 12, and 21 months.

Secondary Patient Reported Outcomes: Sleep Symptoms (Sleep-Related Disturbance and Impairment): We will assess sleep symptoms using the 8-item sleep disturbance and sleep-related impairment scales from the NIH PROMIS set.[71] Dr. Donovan validated these instruments to assess responsiveness to OSA treatment, and found greater responsiveness for PROMIS relative to the standard Epworth sleepiness scale.[72] Together, these measures address the spectrum of sleep symptoms caused by OSA.[73] Global impression of change: We will also have subjects rate their change in symptoms using the single-item patients' global impression of change (PGI-C). PGI-C has been validated in the context of OSA treatment and asks patients to rate their global change in symptoms on a 7 point scale from "1-Very Much Improved" to "7-Very Much Worse".[74] Well-being: We will use a 3-item survey designed to assess Veterans' well-being which assesses overall life satisfaction as well as their ability to be regularly involved and participating in activities that they find important.

5.5.4. Monitoring for eating disorders: In addition to the outcomes outlined above, we will ask participants at 3-month surveys if they have developed symptoms consistent with eating disorders, using Veteran-centric language already in use by VA (https://www.womenshealth.va.gov/WOMENSHEALTH/topics/disordered-eating.asp). If participants indicate that they have developed new symptoms, we will contact them by telephone to confirm their selection. If confirmed, we will encourage them to discontinue any active lifestyle interventions focused on weight loss, and encourage them to discuss these symptoms with their primary care provider. If we are unable to reach participants indicating eating disorder concerns within 1 week, we will send them a letter summarizing the above information.

5.5.5. Physiologic OSA Severity: Including AHI as a secondary outcome measure in this pragmatic trial will be needed to contextualize our intervention's impact for the sleep clinicians and policymakers who continue to rely on AHI as an "objective" marker. We will conduct sleep studies among a subset of participants to compare the impact of the intervention on AHI and estimate the proportion of patients with resolution of detectable OSA. Testing all 696 patients is not feasible in our budget. Therefore, we will select up to n=125 participants in each treatment arm to undergo home sleep apnea testing (HSAT) using level 3 home sleep apnea tests at the

12-month follow up. We will contract with a company, Sleep Care, Inc, to perform these home sleep apnea tests.
We will quantify OSA severity with the apnea hypopnea index, with hypopneas defined using both the 4% and 3% desaturation rules, AHI4% and AHI3%. Of the two, we will prioritize the AHI4% as our measure of highest interest. Prior to distributing tests, we will conduct chart reviews to assess for safety issues that might make pausing treatment for one night unsafe (e.g., severe sleep-related hypoventilation). Following chart review, we will contact patients who expressed an interest at recruitment and are currently using reversible treatments (e.g., CPAP) and ask if they are still interested and able to pause treatment for one night. We will verify safety by asking about daytime sleepiness and any recent heart-related hospitalizations or issues. [222]
We will also contact patients' providers to ensure that OSA treatment can be held for one night to assess untreated sleep. Following the call to the participant and contacting the provider, we will email or fax the patient's contact information to Sleep Care, Inc to arrange delivery and instructions for the HSAT.
If results of the home sleep test reveal a previously unknown concerning result such as severe sleep related hypoxemia (low levels of oxygen), sustained bradycardia (low heart rate), sustained tachycardia (high heart rate), or serious arrythmia such as atrial fibrillation or ventricular tachycardia, study staff will contact the participant and discuss the findings. Study staff will inform the participant that they will also contact the participant's VA primary care provider and/or sleep specialist and make them aware of the finding.

If a participant contacts study staff asking for their HSAT results, a member of the study team will call the participant and review the results with them. We may also mail them a copy of the sleep report if they request it.

We will also assess changes in other markers of respiration and oxygenation and the predictors of these changes. Participants will be compensated $25 for participation in the home sleep test portion of the study.

5.5.6. Implementation Process Evaluation: Consistent with a type I hybrid approach, we will use quantitative and qualitative methods to understand determinants of widespread implementation and other guideline-based treatments for OSA and obesity among Veterans with OSA. This secondary evaluation will be guided by the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework, which is a widely used implementation framework incorporating elements at both the individual and organizational level.[75]

Table 6. Applying RE-AIM to POWER's Implementation Process Evaluation

Element	Definition	Assessment
Reach	The absolute number, proportion, and representativeness of individuals participating in the intervention	- Descriptive statistics of patients nationwide who are eligible, invited, willing to participate, and retained in the intervention or receive other guideline-adherent interventions for OSA and obesity - Among potentially eligible patients, analyze predictors of receiving the intervention and other existing treatments for OSA and obesity - Compare characteristics of participants and non-participants, and participants with intense and sustained participation
Effectiveness	Impact of intervention on outcomes	- Effectiveness outcomes as outlined above for trial population - Use administrative data to assess patient-

		centered outcomes in the wider population of Veterans meeting one or more eligibility criteria who receive guideline-based treatments for OSA and/or obesity
Adoption	Settings and intervention agents who are willing to initiate the intervention	- Qualitative analyses among lifestyle coaches and patients to assess attitudes toward wider adoption of lifestyle interventions and perceived barriers
Implementation	Extent to which the intervention is delivered as intended (fidelity) along with the costs of the intervention	- Qualitative analyses among lifestyle coaches and patients assessing barriers and facilitators to the intervention - Intervention costs and budget impact analysis - Descriptive statistics of fidelity assessments
Maintenance	Long-term effects of the intervention on outcomes after intervention contact	- 21-month effectiveness outcomes for trial population - Long-term patient-centered associated with guideline-based treatments for OSA and obesity - Qualitative analyses among patients assessing barriers and facilitators to sustained lifestyle intervention engagement

5.5.6.2. Data Collection for Qualitative Evaluation of Implementation Process: Eligibility and recruitment for qualitative interviews: Interview participants will include patient participants from the intervention arm and lifestyle coaches. Veteran Patients: Following the end of the intervention and primary outcome collection at 12 months, we will invite intervention participants for qualitative interviews. We will target our recruitment to include participants with a range of contact with the lifestyle coaches and diverse demographic and regional characteristics. We will interview until saturation is reached but anticipate recruiting at least 40 participants to achieve sufficient depth and breadth. Participants will be compensated $25 for participation in the interview. Lifestyle coaches: We will invite all individuals performing lifestyle coaching for a focus-group discussion after intervention conclusion. Qualitative data collection: We will audio record all interviews with a waiver of documentation of informed consent. We will use semi-structured interview guides designed to address RE-AIM domains (Table 6). Guides will include open-ended questions to elicit perceived barriers and facilitators to proactive weight loss care with the lifestyle intervention. Research coordinators trained in qualitative interviews will conduct interviews with patients. Given the close working relationships between lifestyle coaches and research coordinators, qualitative co-investigator will conduct the focus group for lifestyle coaches himself. Recorded interviews will be transcribed.

5.5.6.3. Data Collection for Quantitative Evaluations of Implementation Process: Reach, Effectiveness, and Maintenance: We will collect data for effectiveness (3–12-month outcomes) and maintenance of effectiveness (21-month outcomes) as described above. We may also use VA administrative and PAP usage data from VA approved platforms (e.g., Somnoware) to assess effectiveness and maintenance measures among a nationwide population of Veterans who meet one or more inclusion criteria for the randomized trial. We may also utilize data collected during patient screening and recruitment as well as intervention participation and adherence to inform predictors of reach as outlined in Table 6. In order to compare the reach and effectiveness of our lifestyle intervention relative to existing strategies, we will identify Veterans meeting our criteria for OSA and obesity from FY18 through 23, and query CDW to assess their receipt of evidence-based services and patient centered outcomes in the five years prior and up to two years after OSA diagnosis.

Costs and Budget Impact: Should the intervention be effective, we will conduct a budget impact analysis to establish a business case for future implementation efforts. Analysts will apply the above estimates of higher or lower cost differences between the study arms to project costs for implementing the self-directed lifestyle program nationwide among all VA patients with obesity and OSA. Analysts will estimate the number of VA patients at each site with OSA and obesity who are likely to use our intervention if it were to be rolled out more broadly based on the trial's reach measures and facility-specific Veteran population projections from the VA Enrollee Health Care Projection Model (EHCPM). Sensitivity analyses for subgroups or more targeted rollout strategies will potentially be developed based on discussion with VA operational partners.

Quantifying Costs: Using validated frameworks, we will quantify VA-perspective costs based on A) within-trial costs for implementing the intervention (intervention group only) and B) downstream healthcare utilization (intervention and control).[76,77] Similar to prior VA studies, study staff will log all time spent monitoring adherence and on general intervention support including 1) lifestyle coach training, 2) individual lifestyle coaching activities (e.g. orientation, responding to ad hoc patient requests), and 3) planning.[78] Staff time will be converted to costs based on salaries of the staff conducting the intervention using payroll information. Sensitivity analysis will explore alternative staffing models using estimates from US Bureau of Labor Statistics Occupational Outlook Handbook. Time for research-specific activities including consenting and survey assessments will be excluded. All supply and other material costs will be extracted from intervention fidelity tracking data. To assess potential increases or decreases in longitudinal healthcare utilization, we will compare differences in total utilization in the 24-month period following trial enrollment between the intervention and control groups. Healthcare utilization and total payer costs from will be extracted for all encounters using VA's Managerial Cost Accounting data which is an activity-based allocation system based on payroll and all other care-related expenses (eg. supplies, utilities, service contracts) extracted from VA's general ledger, and any claims patients incur for care delivered in the community that is reimbursed by VA. Confidence intervals for any observed differences in healthcare cost between the intervention and control groups will be estimated using bootstrapping, accounting for distributional assumptions for potentially skewed cost data. Costs will be reported in dollars at the time of reporting final results, with earlier years adjusted for inflation using the Consumer Price Index.

Fidelity: After verbal participant consent, we will audit orientation sessions. We will select a random sample of up to 10 orientations for review per coach. These audits will be spread throughout the year long recruitment. The lifestyle coaches will follow a structured framework for composing messages, which we will sample (randomly select up to 10 messages per month) for periodic quality control review. The coaches will document the frequency, duration, and purpose of phone, MyFitnessPal, and email communications. These records will be subject to periodic reviews.

5.6 Data Analysis

5.6.1 Statistical Power for Primary Outcomes: We designed this pragmatic trial to achieve power of 0.9 for two primary outcomes at 12 months assuming 20% attrition. We target a two-sided type I alpha of 0.025 for each outcome to account for a Bonferroni correction. FOSQ: We plan to detect a meaningful and important difference for FOSQ between groups, 0.75 points,[65] and assume the known standard deviation for change in FOSQ of 2.5 points.[65,79–82] We will retain power of 0.8, even with up to 39% attrition (Table 7). Weight: Participants in D-ELITE's self-directed arm lost 4.5 kg.[41] Assuming weight loss in our comparator group is similar to average Veterans with OSA seeking weight loss, 1.2 kg,[33] we expect a 3.3 kg difference between groups.

This difference approximates a meaningful difference of 3% weight loss (Hoerster et al, JAMA, 2022, PMID: 36511927). Given known standard deviation in clinical weight change among Veterans' attempting weight loss of 6.9 kg/year,[33] we will have 0.99 power to detect this 3.3 kg difference in weight change with 20% attrition (Table 7). We will detect a 2.1 kg difference with power of 0.90. Similar to FOSQ, we retain power even with substantial attrition (Table 7).

Table 7. Power to detect differences in co-primary outcomes

Change in Functional Outcomes of Sleep Questionnaire (FOSQ)					
Power	Alpha	SD (score)	Difference (score)	N	Attrition (%)
0.90	0.025	2.5	0.75	556	20
0.80	0.025	2.5	0.75	426	39
Change in Clinical Weight					
Power	Alpha	SD (kg)	Difference (kg)	N	Attrition (%)
0.99	0.025	6.9	3.3	556	20
0.90	0.025	6.9	3.3	220	68
0.80	0.025	6.9	3.3	170	76
0.90	0.025	6.9	2.1	556	20

5.6.2. Hypothesis Testing for Analyses of Trial Population: We will use intention to treat for analyses of primary and secondary outcomes of consented patients.
H1 (Primary Hypothesis): Lifestyle intervention will lead to greater weight loss and improvement in sleep-related quality of life at 12 months relative to usual care.
H2a (Secondary Hypothesis): Lifestyle intervention will lead to greater improvement in secondary outcomes measured at baseline and follow-up relative to usual care.
H2b (Secondary Hypothesis): Self-directed lifestyle intervention will lead to more favorable values for outcomes only collected at follow up (e.g., AHI, global ratings of change).

Using intention to treat, we will test primary (H1) hypothesis separately for each outcome (weight and FOSQ) using linear mixed effects model

$$Y_{ii} = \beta_0 + \beta_1 T_i + \beta_2 X_i T_i + \beta_3 Q_i + \beta_4 A_i + u_i + \epsilon_{ii}$$

which models for each patient i their measure for each outcome (FOSQ and weight separately), incorporating time of measurement T_j (0 or 12 months), treatment by time interaction $X_i T_j$, stratification variables Q_i, and adjustment variables A_i including age, gender, race, Charlson comorbidity index, and rurality. The model will include a random normal intercept u_i for each patient and a random normal error term ϵ_{ij}, all assumed independent. The variances of the ϵ_{ij} will be assumed different at baseline and 12 months. Here, β_0 is the average baseline FOSQ/weight among the control and treatment groups combined (assumed equal due to randomization), β_1 is the expected change in FOSQ/weight over time in the control group, and β_2 , the quantity of interest in hypothesis H1, is the expected difference in the change in FOSQ/weight over time between the treatment and control groups, or equivalently the expected difference between groups at 12 months. In secondary analyses, we will incorporate primary and secondary outcomes from each time point (baseline, 3, 12, and 21 months). We will use the same model to test secondary outcomes captured only at follow up, omitting baseline values.

Additional Analytic Subgroups:
1) Subgroups defined by each of the pre-specified strata.
2) Subgroups defined by gender.
3) Patients who are prescribed continuous positive airway pressure and use <4 hours per night in the 90 days before the outcome period
4) The subgroup of patients who are prescribed continuous positive airway pressure and use ≥4 hours per night in the 90 days before the outcome period.

5.6.3. Missing and Misclassified Data: Our pragmatic trial prioritizes outcome collection from EMR, including JLV and CAPRI, to reduce participant burden and enhance generalizability. While we attempt to minimize missingness and misclassification through efforts to optimize follow up survey completion and validated approaches to decrease measurement error,[49,83] we anticipate missing data. We originally considered complete case analyses, but ultimately chose an approach based on linear mixed models and maximum likelihood that is valid under the missing at random assumption.[84] Linear mixed models impute missing outcome data implicitly within a hierarchical model, using individuals' baseline, adjustment, and stratification values. Missing values of covariates will be imputed using the chained equations approach (e.g. MICE),[85] using single imputation if missing rates are less than 5% and multiple imputation otherwise. We will carry out the recommended sensitivity analyses to the MAR assumption using methods based on pattern mixture models and imputation, by assuming a range of perturbations of imputed outcome values and assessing differences in model conclusions.[85,86]

5.6.4. Analysis for Qualitative and Quantitative Evaluations of Implementation Process:

Reach, Effectiveness, and Maintenance: We will compare those with OSA who are invited to the trial and enroll vs. those who do not. We will assess effectiveness and maintenance of effectiveness at 12 and 24 months in the trial population (Section 5.6.1-5.6.2). We may also use VA administrative and PAP usage data from VA approved platforms (e.g., Somnoware) to assess predictors and consequences of receiving our intervention or other guideline-based therapies for OSA and obesity among Veterans nationwide who meet one or more inclusion criteria for the randomized trial.

Costs and Budget Impact Analysis: We will record intervention costs and conduct a budget impact analysis to establish a business case for future implementation, should the intervention be effective. We will compare mean cost differences between trial arms using linear models (Model 1) like our co-primary outcomes, ensuring model assumptions are met for cost data with appropriate transformations. *Budget Impact Analysis*: Should the intervention be effective, we will conduct a budget impact analysis to establish a business case for future implementation efforts. Analysts will apply the above estimates of higher or lower cost differences between the study arms to project costs for implementing the self-directed lifestyle program nationwide among all VA patients with obesity and OSA. Analysts will estimate the number of VA patients at each site with OSA and obesity who are likely to use our intervention if it were to be rolled out more broadly based on the trial's reach measures and facility-specific Veteran population projections from the VA Enrollee Health Care Projection Model (EHCPM). Sensitivity analyses for subgroups or more targeted rollout strategies will potentially be developed based on discussion with VA operational partners.

Qualitative Data Analysis: We will analyze transcripts using simultaneous inductive and deductive content analysis.[87] Inductive content analysis consists of open (unstructured) coding,

allowing for the emergence of previously unidentified themes. In contrast, deductive content analysis is structured and consists of identifying themes that fit within *a priori* categories. *A priori* categories will be based on RE-AIM domains, and we will use quotes that do not accurately fit within existing a priori codes to iteratively develop novel codes. We may use ATLAS.ti analysis software for recording and managing codes. The project team will review the results of the analytic process to assess completeness.

5.7 Withdrawal of Subjects

We do not anticipate a need to withdraw a participant from the research entirely. If a participant becomes pregnant, we become aware of a serious physical or mental health issue, or the participant's primary care provider notifies us that the individual should not continue the intervention, the participant will cease participation in the intervention activities of the research; however we will continue to follow the individual through completion of the study via CDW and self-report.

If a participant chooses to withdraw him/herself from the research, we will confirm with the individual that we may continue to follow him/her in CDW. If the individual declines, we will respect his/her choice and not collect additional data from CDW; however we will use any data collected up to the date of withdrawal.

For the purposes of follow-up, we will consider an individual "lost to follow up" if we are unable to collect either primary 12-month endpoint.

6.0 Reporting

6.1 Quality monitoring

The investigators will closely monitor and prepare annual summary reports on:

- Patient accrual and follow-up completion/retention in relation to goals and timeline.
- Randomization process and group comparability on the balancing variables.
- Key baseline characteristics of the sample, by blinded group, on the primary and secondary outcome variables.
- Intervention adherence.
- Protocol violations.

6.2 Data Safety and Monitoring Board.

This study will be reviewed regularly (at least annually) by a DSMB convened by the national director of VA HSR&D. This board will monitor the quality of data, progress of recruitment, as well as the incidence of adverse events between arms.

6.3.1. Adverse event monitoring.

To ensure unbiased determination across treatment arms, at 12- and 21-month follow-up contact we will ask participants to complete a survey about potential adverse events (AE), serious adverse events (SAE) and unanticipated problems (UP) employing a body system-based assessment. We define SAEs as those requiring hospitalization or death.

Study staff will collect adverse events using participant self-reports collected at 12 and 21 months. Study staff will also perform chart reviews looking for discharge summaries for the 12 month time period. Study staff will later complete additional chart reviews looking for discharge

summaries for the 21 month time period among patients who do not complete 21 month surveys. Dr. Donovan or another clinician will assess each AE for duration (start and stop dates and times), expectedness in the study population, severity, outcome, treatment, and relation to study activity.

To account for potential differential survey response rates by arm, we will also query the electronic medical record and compile hospital admissions from randomization through 24 months post randomization. We will report the number of hospitalizations by arm to in our final DSMB report.

The following are expected adverse events in the POWER population of participants who have obstructive sleep apnea, a high BMI, and adopt healthy eating and physical activity program:

- Gastrointestinal symptoms related to change in diet.
- Musculoskeletal symptoms or injury resulting from increased physical activity, including increasing symptoms such as chest discomfort, shortness of breath, and leg cramping.
- Development of weight and OSA associated medical disorders including diabetes, hypertension, liver disease, cardiovascular disease, cerebrovascular disease, arrythmias, asthma, COPD, clotting problems, and other lung related conditions;
- Development or exacerbation of mental health conditions, the worsening of which is known to be associated with poor sleep, including depression, anxiety, posttraumatic stress disorder, and bipolar disorder.
- Development or exacerbation of eating disorders including binge eating disorder, anorexia nervosa, and bulimia nervosa.
- Development of other conditions associated with unhealthy health behaviors, such as from tobacco and alcohol disorders (e.g., cancer).
- Age related illnesses, such as pneumonia, urinary tract, and skin infections.
- Motor vehicle collision or other accidents arising from excessive sleepiness.
- Death

Upon discovering an unexpected and related SAE, study staff will provide the IRB and DSMB with a report describing the duration (start and stop dates and times), severity, outcome, treatment, and relation to study activity, according to the required timelines. The DSMB may request additional information if it deems additional deliberation is warranted.

For all other events, staff will summarize and report to the DSMB on an annual basis the numbers and types of all AEs by unidentified treatment arms. At their discretion, the DSMB may request unblinded results to determine the nature and extent of effect of the intervention. Should the DSMB make this request, we will maintain blinding of the investigators and the staff involved in follow-up data collection and analysis. If, at any time, the investigators believe they are seeing an unexpected increase in SAEs that is a cause of concern, they will bring this to the attention of the DSMB.

For annual reporting, staff also will provide the quality monitoring report to the DSMB.

At the annual meeting, the DSMB will review AE/SAEs and the quality of data, as well as review study progress and provide objective recommendations, as appropriate, with respect to:

- Determination of any actions to be taken in response to SAEs.
- Reports related to study operations and the quality of the data.
- Consideration of early termination of the study because of treatment safety concerns or inadequate performance.
- Modifications in the study protocol concerning recruitment, participant retention, data quality, outcome assessment, statistical analysis, or general trial operations.

7.0 Privacy and Confidentiality

This study will use PHI.

To ensure the data are secure, the study team will code study data with a unique study code. We will maintain the master list separately from the study data. The researchers will maintain data on the VA HSR&D network in password protected and permission specific directories and databases. Our network has multiple levels of protections and access is restricted to IRB-approved staff. If a staff member leaves the study, we will remove his/her permissions to access the data. We will follow all VA HSR&D data security policies.

Paper copies will be stored in a secure office suite in locked files accessible by approved study staff only. The ISO and Privacy Officer will be notified within one hour of the improper use or disclosure, as well as any other local policies.

All study information is accessible only by IRB approved study staff on a need-to-know basis.

To report study results, we will use only aggregate data.

The study team considers all participant information confidential. We will share information with participants' physicians only as needed to protect participants' safety. We inform the participant of this practice as part of the informed consent process.

We will offer participants the option of tracking their diet and exercise through MFP, which is a publicly available web-based platform. The loss of privacy with MFP is no greater than the risk of ordinary use of numerous similar publicly available online programs. As part of informed consent decision-making, we will describe this risk, as well as the potential benefits of participating in an intervention with demonstrated effectiveness and safety in other populations. With that in mind, participants can choose if they wish to use MFP and/or a paper tracker.

We also offer participants the option of responding to questionnaires via Qualtrics, a web-based survey platform licensed by VHA ORD. The loss of privacy with Qualtrics is no greater than the risk of responding to questionnaires on paper and by mail. As part of the informed consent decision-making process, we will describe the process of responding to online questionnaires. Participants will also have the option to utilize paper questionnaires instead. Survey links sent via unencrypted email or text message will <u>not</u> contain PHI. Emails or text messages containing mention of the POWER study will be encrypted (if emailed) and conform to VA data security policy. Incoming emails or text messages may either be bounced back to the sender as nondelivered, or an automatic response may contain an out-of-office and unmonitored message. Telephone number and supported carriers (i.e., T-Mobile, Verizon, AT&T, etc.) may be confirmed

prior to delivering text messages via e-mail. We may also send out “batch” texts via Qualtrics to participants with a phone number on file. These batch texts will use the texting template and include an option to not receive links via text in the future. Responses stored on Qualtrics servers will be associated with a unique study code, password protected, and encrypted.

We will share contact information with a contracted company, Sleep Care, Inc, for a subset of participants to undergo at home sleep apnea testing.

8.0 Communication

This is a single-site study. To ensure all elements of the study protocol are followed and that study goals are met, the project manager will conduct regular meetings with project staff to review study procedures and status, barriers encountered, and develop responses to any identified issues.

Study staff will send participant contact information to Sleep Care, Inc via either encrypted email or secure fax. Sleep Care will contact participants using the contact information provided, first attempts will be by phone followed by HIPAA compliant email or text if the participant has provided cell phone or email contact. Sleep Care will send the collected sleep data via reports either by secure email or fax.

9.0 Information Security and Data Storage/Movement

POWER staff will store paper-recorded data in secure, locked file cabinets within HSR&D secure office suite, and electronic data in password protected files on secure VA network servers or VA Office of Information and/or Technology (OI&T) managed archived back-up media. Online questionnaire responses collected through the Qualtrics platform are stored on password protected and encrypted servers. Qualtrics is FedRamp authorized, and all data will remain property of ORD. All electronic data will be stored according to VA data security policy. Our network has multiple levels of protections and access is restricted to IRB-approved staff. Limited analytic datasets are shared between authorized study personnel via secure transmission and/or via a secure virtual private network employing industry-standard password protection and data encryption. Study data is not disclosed to any third party except as required by law.

A limited amount of contact information is provided to Qualtrics to allow the provider to distribute unique anonymized survey links. Information is transmitted to Qualtrics via secure, encrypted, web-based portal.

We will also contract with a company, Sleep Care, Inc, to perform home sleep apnea testing among a subset of subjects in our trial. The company coordinate with the participant to mail home sleep apnea tests to these patients, collect the tests by mail, and will return data around their home sleep apnea testing results to the POWER team through secure means (e.g., secure fax, encrypted email). We will ensure that data transferred between the POWER team and the contracting company is accomplished through methods approved by privacy and ISSO as part of the contracting process.

Once the study is closed, we will retain these research data for the minimum period required for records retention in accordance with the National Archives and Records Administration (NARA) VHA Record Control Schedule (RCS). The VAPSHCS Research and Development Office will be responsible for overseeing the storage of the data during the RCS required records retention period and for the eventual destruction of the data as authorized by the RCS. When the minimum data retention period has ended, all research data records in the possession of VAPSHCS will be destroyed. At this same time, we will also work with VINCI staff to destroy these records from any VINCI server(s) and archived tape backups/media. For electronic data, the Office of Information and Technology (OI&T) is responsible for maintaining the security of the electronic records during the records retention period. The data will be destroyed by a method to be determined by the VAPSHCS Information Security Officer (ISO) in a manner that is compliant with VA Handbook 6500.1 and National Institute of Standards and Technology NIST SP 800-88.

Study staff will enter all study data into SQL databases housed within HSR&D. Data collected via Qualtrics will be regularly downloaded and assimilated into SQL databases. All the data entry systems will employ automatic, real-time range, logic, and missing value checks. We will employ double data entry and logic controls to minimize data entry error. We will maintain one official copy of all the study data and a master data dictionary.

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