Respiratory Effects of Dose Optimization Under Comprehensive Opioid Management (REDUCE)

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Respiratory Effects of Dose Optimization Under Comprehensive Opioid Management (REDUCE)

Study Description: This study is a Phase II, single-center, randomized, controlled, parallel-group trial designed to evaluate the effects of referral to the UC San Diego Opioid Management Program, compared with usual care, on ventilatory stability and sleep-disordered breathing physiology in adults with chronic opioid use. Participants will be randomized to either usual care or referral to the UC San Diego Opioid Management Program and followed for approximately 26 weeks. Participants referred to the UC San Diego Opioid Management Program will receive individualized Comprehensive Opioid Management provided by their treating clinician or designated opioid management provider in accordance with usual clinical practice guidelines. Comprehensive Opioid Management may include changes to opioid therapy and other pain-management strategies when clinically appropriate. The research team will not prescribe opioids or direct opioid dose adjustments, and no opioid dose adjustments are required by the study protocol.

Objectives:

Primary Objective: To determine whether guideline-concordant, clinician-directed Comprehensive Opioid Management improves ventilatory stability in adults with chronic opioid use and sleep-disordered breathing compared with usual care.

Secondary Objectives: To evaluate the effects of guideline-concordant, clinician-directed Comprehensive Opioid Management on sleep-disordered breathing severity, respiratory pattern variability, sleep gas exchange, nocturnal hypercapnia, psychomotor vigilance, patient-reported sleep outcomes, pain-related outcomes, and opioid exposure.

Endpoints:

Primary Endpoint: Change in ventilatory instability as measured by loop gain.

Secondary Endpoints: Secondary endpoints include apnea–hypopnea index (AHI), flow-based apnea–hypopnea index (AHIflow), respiratory pattern variability, oxygen saturation metrics including time spent with SpO_2 <90%, transcutaneous carbon dioxide ($TcCO_2$), psychomotor vigilance testing (PVT), patient-reported sleep and symptom measures, pain-related outcomes, and opioid levels/exposure.

Study Population: Adults aged 18–75 years with chronic opioid use for ≥3 months, opioid dose ≥20 morphine-equivalent dose per day (MEqD), and sleep-disordered breathing defined as AHI ≥5 events/hour.

Phase: Phase II

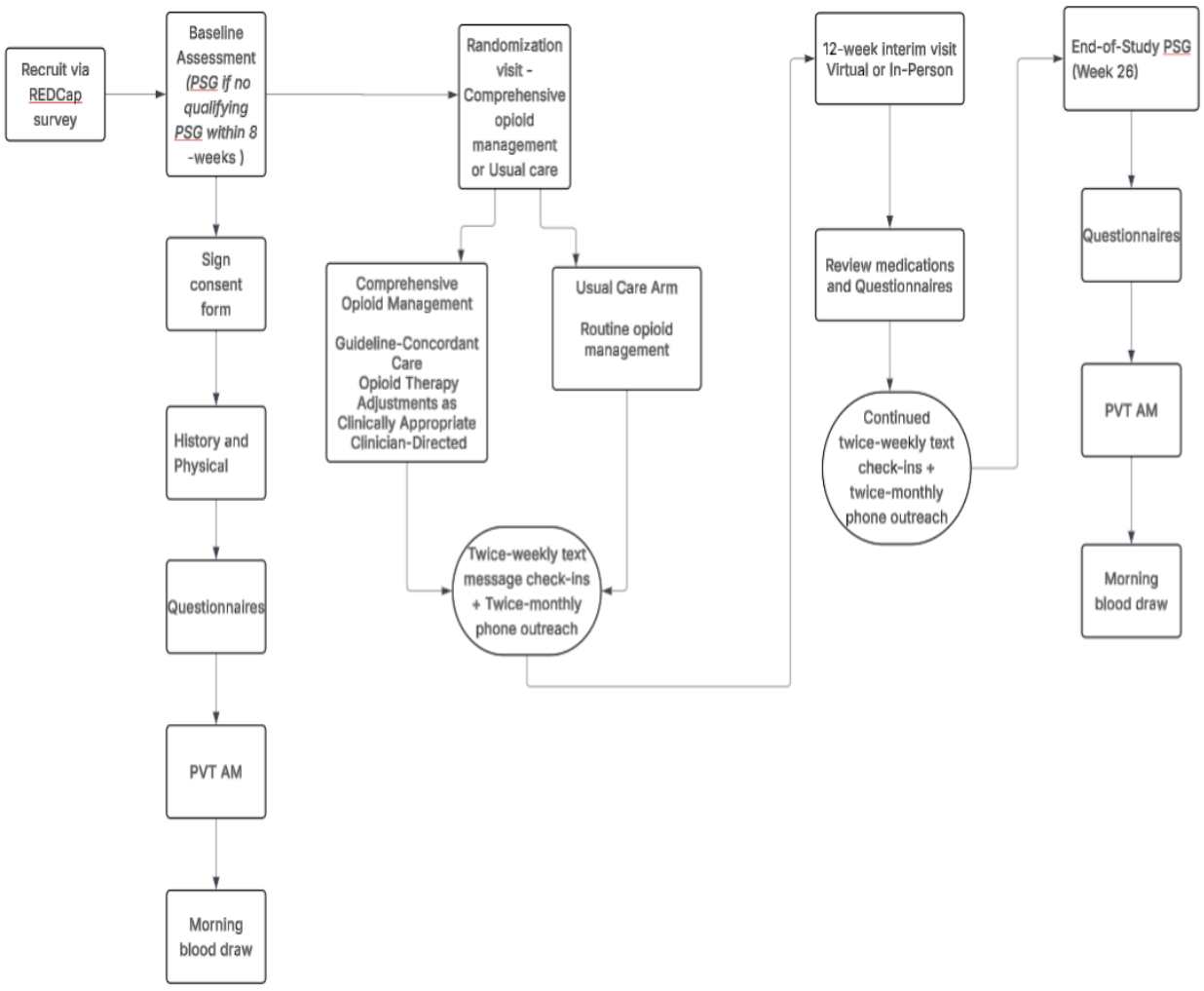
Description of Sites/Facilities Enrolling Participants: Participants will be enrolled through UC San Diego clinical practices and all study procedures will be conducted at UC San Diego Sleep Research and Clinical Research facilities.

Description of Study Intervention: Guideline-concordant, clinician-directed Comprehensive Opioid Management compared with usual care in a randomized parallel-group design. The Comprehensive Opioid Management intervention may include changes to opioid therapy, medication management, and other pain-management strategies, as determined by the participant's treating clinician and consistent with clinical practice guidelines.

Study Duration: 5 Years

Participant Duration: Approximately 26 weeks per participant

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	**Baseline (Can be done at overnight)**	**Randomization Visit**	**Treatment Period (Weeks 0–26) (Usual Care OR** comprehensive opioid management **Arm)**	**12-week Interim visit**	**End-of-Study PSG (Week 26)**
Informed consent	X				
Demographics	X				
Medical and sleep history	X			X	X
Concomitant medications review	X	X	X[2]	X	X
Inclusion/exclusion review	X	X			
Physical examination	X				
Vital signs (BP, HR, RR, SpO_2)	X				X
Height / weight / BMI	X				X
Urine pregnancy test (participants of childbearing potential)	X				
Questionnaires	X			X	X[1]
PSG	X[1]				X
Randomization		X			
Adverse event review	X	X	X	X	X
Safety Monitoring Contacts			X[2]		
Opioid use assessment	X	X	X	X	X
AM psychomotor vigilance testing (PVT)	X				X
Blood draw / opioid levels	X				X

1- If not done in the last 8 weeks

2- Participants will receive twice-weekly text-message safety check-ins, including assessment of opioid withdrawal symptoms using the Subjective Opiate Withdrawal Scale (SOWS), and twice-monthly telephone outreach during the 26-week treatment period. Telephone outreach may also occur in response to concerning, absent, or worsening check-in responses.

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic opioid use is increasingly recognized as a contributor to sleep-disordered breathing (SDB), including both obstructive and central sleep apnea. Opioids can alter ventilatory control by suppressing respiratory drive, increasing ventilatory instability, and impairing physiologic responses to hypoxia and hypercapnia. These effects may contribute to increased apnea–hypopnea burden, oxygen desaturation, nocturnal hypercapnia, and sleep fragmentation.

This study will evaluate whether guideline-concordant, clinician-directed Comprehensive Opioid Management improves ventilatory stability and sleep-disordered breathing physiology compared with usual care. This intervention incorporates individualized opioid and pain-management strategies, determined by the participant's treating clinician, to address potentially modifiable contributors to ventilatory instability. Participants will be randomized to either usual care or a Comprehensive Opioid Management intervention and followed for approximately 26 weeks.

2.2 BACKGROUND

The opioid epidemic is an ever-accelerating public health issue in the USA (Figure 1) (1-4). Increases in opioid use were noted in the 1990s, driven by several political, social, and demographic factors (5-11). Despite being labeled as a public health emergency in 2017, opioid-related deaths have continued to increase, with most recent data finding over 81,000 deaths in 2023 (12). While a substantial proportion of deaths are related to illicit synthetic opioids, adverse effects of prescription opioid use play an important direct and indirect role in driving the ongoing crisis. Even under medical supervision, opioid use is associated with an increased risk of death (13) potentially via increased arrhythmia and sudden death (14), cardiovascular disease (15-19), respiratory infections (20), and therapeutic misadventures (13).

Opioids are – and will remain – a mainstay in modern medical care. In the setting of chronic pain, opioids remain a CDC guideline-supported intervention for refractory pain (21). A commonly cited Cochrane meta-analysis found that while escalating opioid doses were not associated with better pain control, the effectiveness of sustained therapy has not been disproven (22). Other metanalyses have found modest improvements in pain and physical functioning with opioids compared to non-opioid pharmacotherapy (23). Clinical practice has reflected that carefully adjusted long-term opioids might be warranted for some individuals; the incidence of new prescriptions and average dose of opioid per prescription dose has decreased (Figure 1), while the average duration of opioid use has increased (24, 25). In terms of opioid use disorder (OUD), medications for OUD (e.g. methadone, buprenorphine) have been shown to substantially reduce relapse and death but are nonetheless opioids (26). In the setting of palliative care (particularly oncology), opioids are often used long term for pain and dyspnea, i.e., not just at immediate end-of-life. With increasing therapeutic options for advanced cancer leading to improved survival, maintaining pain control without compromising outcomes is imperative. Overall, there is a need for safe prescribing, monitoring, and therapeutics to mitigate adverse impacts related to opioids.

Opioids are well-known to have impacts on breathing. In the setting of acute administration, opioid-induced respiratory depression (OIRD) is a major concern (27). OIRD is characterized by a reduction in level of consciousness and suppression of breathing that can lead to arrest. OIRD is typically an acute

phenomenon in the setting of opioid overdose; nonetheless, OIRD is not the only respiratory manifestation of opioid use.

People using long-term opioids have an increased risk of sleep disordered breathing (SDB). Although estimates vary, data suggest up to 50% of patient using opioids have evidence of central sleep apnea (CSA) (28-33) with a dose-dependent but highly variable relationship to opioids. OSA is also a very common disease with major health impact (34-45). In those with OSA, opioids contribute to central apneas and worsened hypoxemia (46-48), and are a well-established risk factor for failure of first-line continuous positive airway pressure (CPAP) treatment due to emergent and persistent respiratory events (49-52). Overall, opioids appear to contribute to the severity and complexity of SDB (47, 53-64).

In general, continuous positive airway pressure (CPAP) is the first-line treatment for SDB. The major effect of CPAP is in stabilizing the upper airway (65) although decreased hypoxemia and blunted changes in CO_2 can contribute to stability of respiratory control (65-72). In otherwise healthy individuals, these effects often lead to resolution of OSA in but may lead to improvements in CSA as well, best studied in heart failure (73). On the other hand, CPAP may unmask central apneas via alleviation of restricted ventilation from upper airway obstruction (74-81). Observational studies implicate opioid use as a strong risk factor for development and persistence of CSA during use of CPAP, termed treatment-emergent CSA (51, 52). Overall, CPAP has been observed to have variable effects in opioid related SDB (82-85).

Given these limitations on CPAP efficacy, along with challenges with long term adherence with similar devices (e.g., BIPAP), targeted strategies are needed to address SDB related to opioid use (86). While complete *elimination* of opioids may serve to reverse the complexity of SDB (87, 88), in practice this goal can be difficult to achieve. Indeed, population studies suggest despite some reductions in opioid initiation, mean duration of opioid use appears to be increasing (25). More realistic goals include opioid dose *reduction*, which is supported by CDC recommendations (21). However, randomized trials of slow dose reduction have shown successful reduction of opioid doses over a 6-month timeframe but been variable in terms of individual-level short-term symptomatic benefit (89-91). Similarly, there are currently no published studies that have examined the effect of dose reduction on SDB; the effects of dose reduction on SDB and attendant outcomes are likely to differ based on the extent to which opioid-induced ventilatory instability is driving SDB.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Participants may experience risks associated with study procedures, including discomfort or sleep disruption during overnight polysomnography, mild skin irritation from monitoring sensors, temporary sleepiness following overnight testing, discomfort or bruising from blood collection, and emotional discomfort when answering questionnaires about pain, mood, sleep, or opioid use.

This study does not require opioid dose reduction. However, participants randomized to the Comprehensive Opioid Management group may have opioid or other pain-management changes recommended by their treating clinician or designated opioid management provider as part of routine clinical care. These treatment decisions are not directed by the research team. Clinically indicated changes

in opioid therapy may result in worsening pain, opioid withdrawal symptoms, mood changes (including depression or suicidal thoughts), reduced physical functioning, respiratory changes, or other clinical instability. These risks may also occur in participants receiving usual care if their treating clinician independently recommends changes to their treatment. The UC San Diego Opioid Management Program is an existing clinical program and does not use a research-specific opioid treatment pathway for study participants. Participants referred through this study receive the same usual clinical care that would be provided to other patients seen by the program. The research team does not prescribe opioids or direct clinical treatment decisions. Study-specific safety monitoring is conducted in accordance with the Data and Safety Monitoring Plan and includes assessment of adverse events, serious adverse events, opioid withdrawal symptoms, pain control, mood symptoms including suicidality, sedation, respiratory symptoms, emergency care utilization, medication changes, and other clinically significant changes in health status.

There is also a small risk of loss of confidentiality despite safeguards to protect participant information. Although unlikely, research testing may identify previously unrecognized medical conditions, including sleep-disordered breathing or other clinically important findings that may require referral for additional clinical evaluation and treatment.

Details regarding risks are provided in DSMP §3.2.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may or may not receive a direct benefit from participating in this study. Possible benefits include identification of previously unrecognized sleep-disordered breathing or other clinically important findings that may require follow-up with their healthcare provider. Participants randomized to the Comprehensive Opioid Management group may also experience improvements in pain management, opioid therapy, breathing during sleep, or overall health if clinically appropriate treatment changes are made by their treating clinician or designated opioid management provider. Information gained from this study may improve understanding of the relationship between opioid management and sleep-disordered breathing and may help improve the care of future patients with chronic opioid use and sleep-disordered breathing.

Details regarding benefits are provided in DSMP §3.1.

Payment to participants is not considered a benefit.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The risks associated with this study are considered reasonable in relation to the potential benefits and the importance of the knowledge to be gained. Potential risks include discomfort or sleep disruption from overnight polysomnography (PSG), morning drowsiness or impaired vigilance after overnight research procedures, blood draw discomfort or bruising, questionnaire-related emotional distress, loss of confidentiality, and identification of previously unrecognized sleep-disordered breathing or other clinically important findings requiring notification or referral. Participants assigned to the Comprehensive Opioid Management group may also experience worsening pain, opioid withdrawal symptoms, mood changes (including suicidality), functional decline, or other clinical destabilization associated with

clinician-directed opioid dose adjustments. These risks will be minimized through guideline-concordant clinical care, oversight by the participant's treating clinician or designated opioid management provider, regular participant contact, safety monitoring, trained study staff, standard study procedures, secure data systems, and appropriate follow-up of clinically significant findings.

Potential benefits of participation are not guaranteed. Participants may benefit from identification of previously unrecognized sleep-disordered breathing or other clinically important findings requiring notification or referral. Some participants may experience short-term physiologic benefit from clinician-directed opioid dose adjustments as part of Comprehensive Opioid Management. The knowledge gained from this study is expected to improve understanding of ventilatory control, sleep-disordered breathing, opioid-related respiratory physiology, and the mechanisms underlying these conditions, and may inform future treatment strategies.

Overall, the anticipated risks are considered reasonable in relation to the potential benefits and the importance of the knowledge expected to be gained.

Details regarding protections against risk are provided in DSMP §3.

Details regarding monitoring procedures and frequency are provided in DSMP §4.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the effect of guideline-concordant, clinician-directed Comprehensive Opioid Management on ventilatory stability in adults with chronic opioid use and sleep-disordered breathing compared with usual care.	Change in ventilatory instability as assessed by polysomnographic measures, including loop gain.	Loop gain is a key physiologic measure of ventilatory control and instability and reflects the underlying mechanisms of sleep-disordered breathing. It is an appropriate primary endpoint to evaluate the effects of Comprehensive Opioid Management on respiratory control
To evaluate the effects of guideline-concordant, clinician-directed Comprehensive Opioid Management on sleep-disordered breathing severity, gas exchange, ventilatory control, neurobehavioral	Apnea–hypopnea index (AHI), flow-based apnea–hypopnea index respiratory pattern variability, arousal threshold, oxygen saturation metrics (including time spent with SpO_2 <90%),	These endpoints assess both physiologic and clinical outcomes, including ventilatory control, sleep-disordered breathing severity, gas

performance, pain-related outcomes, and patient-reported outcomes.	transcutaneous carbon dioxide ($TcCO_2$), psychomotor vigilance testing (PVT), patient-reported sleep outcomes, pain-related outcomes, and opioid exposure levels.	exchange, and functional outcomes. They allow a comprehensive evaluation of the effects of Comprehensive Opioid Management on respiratory physiology and patient-centered outcomes.
To explore factors associated with response to Comprehensive Opioid Management, including baseline physiologic characteristics, opioid exposure, and clinical variables.	Associations between baseline physiologic measures and changes in loop gain, sleep-disordered breathing severity, gas exchange, and functional outcomes.	These analyses may help identify predictors of response to Comprehensive Opioid Management and provide insight into mechanisms underlying variability in treatment response.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is designed to evaluate the extent to which Comprehensive Opioid Management, including clinically appropriate changes in opioid therapy over time, improves ventilatory stability and sleep-disordered breathing physiology in adults with chronic opioid use and sleep-disordered breathing compared with usual care. The research team will not prescribe opioids or independently direct opioid therapy changes. Opioid prescribing and treatment-management decisions will remain under the participant's treating clinician or designated clinical opioid management provider. Comprehensive Opioid Management will be conducted in accordance with clinical practice guidelines and individualized to each participant's clinical needs.

This is a Phase II, single-center, randomized, controlled, parallel-group trial conducted at the University of California, San Diego. Participants will be randomized to one of two study groups: usual care or referral to a clinically supervised Comprehensive Opioid Management program.

Participants assigned to usual care will continue opioid management with their treating physician. Participants assigned to the Comprehensive Opioid Management arm will be referred to the UC San Diego Opioid Management Program (director and study co-investigator: Dr. Deanna Hill). This program will assume opioid management and will follow its usual clinical protocols, including a comprehensive assessment of opioid use and pain control, and may incorporate changes to opioid therapy and other pain-management strategies when clinically appropriate.

For the purposes of research, participants will undergo screening and baseline assessments to determine eligibility, including informed consent, medical and sleep history, physical examination, questionnaires, concomitant medication review, opioid use assessment, and opioid level collection, if applicable. Eligibility will include confirmation of chronic opioid use and sleep-disordered breathing.

The UC San Diego Opioid Management Program is a relatively new clinical program directed by Dr. Deanna Hill, UC San Diego Clinical Professor. Dr. Hill currently sees patients for this program one day per week within her UC San Diego Health Primary Care Clinic. The program provides specialty clinical care to assist with opioid management for patients with chronic pain and assumes opioid management while clinically appropriate and achievable adjustments to the patient's opioid regimen are addressed. Once the patient's opioid regimen is clinically stable and appropriate management goals have been addressed, opioid-prescribing responsibility may transition back to the referring clinician.

Because this is a relatively new clinical program, formal program-level data regarding success rates and patient withdrawal/discontinuation rates are not yet available. Anecdotally, most patients participate in regular clinical follow-up while the program is managing their opioid prescriptions. There is no single definition of program "success," because appropriate treatment goals and management strategies are individualized and may include opioid dose optimization, medication changes, non-opioid pain-management strategies, stabilization of pain control, or other clinically appropriate interventions.

Referral to the program may be placed in Epic through an Internal Medicine referral by selecting "Pain Consult." For patients with non-HMO insurance, a formal referral is generally not required. Patients with HMO insurance who receive primary care at UC San Diego require referral from their primary care physician. Participants randomized to Comprehensive Opioid Management will be assisted with referral as appropriate based on their insurance and clinical circumstances.

Participants will complete either one or two overnight polysomnography (PSG) visits during the study. A baseline PSG will be performed only if a qualifying PSG has not been completed within 8 weeks of enrollment. Participants who have completed a qualifying PSG within 8 weeks of enrollment will not undergo a repeat baseline PSG. Baseline PSG assessments may include standard PSG measures, oxygen saturation, and transcutaneous carbon dioxide ($TcCO_2$).

Following completion of baseline assessments, eligible participants will be randomized to either usual care or Comprehensive Opioid Management. If the baseline visit and randomization cannot be completed on the same day, participants may return for a separate daytime randomization visit before beginning the study intervention.

Participants will then enter a 26-week follow-up period. During this period, participants will complete twice-weekly text-message safety check-ins and twice-monthly telephone outreach. Additional telephone outreach may occur if participants report concerning or worsening symptoms, fail to respond to scheduled safety check-ins, or if additional follow-up is needed to assess participant safety or study participation. Safety contacts will assess current opioid use, medication changes, adverse events, withdrawal symptoms, pain control, mood symptoms including suicidality, respiratory symptoms, emergency care utilization, and study adherence. Same-day PI review will occur when indicated according to the DSMP escalation criteria.

An interim visit at Week 12 will include assessment of current opioid use and completion of study questionnaires.

At the end of the 26-week treatment period, all participants will return for a follow-up visit and an end-of-study PSG, regardless of whether a baseline PSG was required. Therefore, participants will complete either one overnight PSG (if they have a qualifying baseline PSG completed within 8 weeks of enrollment) or two overnight PSGs (if a baseline PSG is required). The follow-up visit will include a medical history update, physical examination, questionnaires, opioid use assessment, and opioid level collection, if applicable. The end-of-study PSG will include standard PSG measures, oxygen saturation, and $TcCO_2$ monitoring.

If an in-person assessment cannot be completed during a scheduled visit, or if additional study data need to be collected or repeated, participants may be asked to return for an additional daytime visit. If data from a baseline or end-of-study PSG are incomplete or technically inadequate for interpretation, participants may be asked to complete one additional overnight PSG to obtain sufficient study data for analysis.

The primary assessment will compare changes in ventilatory stability between participants randomized to usual care and those randomized to Comprehensive Opioid Management over the 26-week study period. Secondary assessments will evaluate sleep-disordered breathing severity, gas exchange, neurobehavioral performance, patient-reported sleep outcomes, pain-related outcomes, and opioid exposure.

Participant compensation

- Baseline visit without PSG: $50
- Baseline Visit with Overnight PSG, if needed: $200
- Randomization Visit, if a separate visit is needed: $50
- Safety monitoring contacts (twice-weekly text-message check-ins and twice-monthly telephone outreach): $5 per completed check-in, up to a maximum of $10 per week
- Interim visit: $50
- End-of-Study Overnight PSG (Week 26): $200
- If an additional daytime visit is needed for data collection: $50
- If data are inconclusive and an additional polysomnography night is required, participants will receive an additional $200.

No formal interim efficacy analysis is planned. Safety data will be monitored throughout the study, including adverse events, serious adverse events, withdrawal symptoms, pain control, and clinically significant changes in health status. No additional sub-studies are included in this protocol.

Details regarding protections against risk are provided in the DSMP §3.

Details regarding monitoring procedures and frequency are provided in the DSMP §4.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

A randomized, controlled, parallel-group design was selected to evaluate the effects of Comprehensive Opioid Management on ventilatory stability and sleep-disordered breathing physiology in adults with chronic opioid use.

A parallel-group design allows evaluation of changes in physiologic and clinical outcomes between participants undergoing Comprehensive Opioid Management and those receiving usual care. A control group, rather than a single-arm pre-post design, helps reduce bias related to secular trends, regression to the mean, and learning effects.

The 26-week study period allows sufficient time for implementation of Comprehensive Opioid Management and assessment of associated changes in ventilatory control, sleep-disordered breathing, and patient-centered outcomes. Safety monitoring contacts, including twice weekly text-message safety check-ins and twice-monthly telephone outreach, support monitoring of participant status and safety throughout the study period.

Baseline and end-of-study polysomnography, together with physiologic and clinical assessments, enable evaluation of ventilatory instability, sleep-disordered breathing severity, gas exchange, neurobehavioral performance, and functional outcomes.

4.3 JUSTIFICATION FOR DOSE

The study intervention is guideline-concordant, clinician-directed Comprehensive Opioid Management compared with usual care. Participants randomized to the usual care arm will continue opioid management under the direction of their treating clinician.

Participants randomized to the Comprehensive Opioid Management arm will receive individualized opioid and pain-management care under the supervision of their treating clinician and/or designated opioid management provider. Comprehensive Opioid Management will be conducted in accordance with clinical practice guidelines and may include changes to opioid therapy, medication management, and other pain-management strategies, as clinically appropriate.

The research team will not prescribe opioids or independently direct opioid therapy changes. All opioid prescribing and treatment-management decisions will remain under the participant’s treating clinician or designated opioid management provider.

Participants will be followed for approximately 26 weeks. During this period, opioid use, medication changes, withdrawal symptoms, pain control, adverse events, and clinically significant changes in health status will be monitored through scheduled study contacts and safety assessments.

No investigational drug product is administered as part of this study. The comparator condition is usual care, in which opioid management remains under the participant's treating clinician.

4.4 END OF STUDY DEFINITION

The end of the study for an individual participant is defined as completion of the Week 26 end-of-study visit and final polysomnography (PSG), including all required study assessments.

The end of the study globally is defined as the date on which the last participant completes the final end-of-study visit and all associated procedures, including the final PSG and required follow-up assessments.

Participants who discontinue the study early will be considered to have reached the end of study at the time of their final completed study visit, and efforts will be made to complete end-of-study assessments, when feasible.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants must meet all of the following criteria to be eligible for enrollment:

1. Age 18 to 75 years
2. Chronic opioid use for ≥3 months with a daily dose ≥20 mg oral morphine-equivalent (MEqD)
3. Diagnosis of sleep-disordered breathing (SDB), defined as AASM-recommended apnea–hypopnea index (AHI3A) ≥ 5 events per hour on a qualifying sleep study. AHI3A includes hypopnea definition ≥ 30% airflow reduction lasting ≥ 10seconds, accompanied by ≥3% SpO2 desaturation or arousal.
4. Ability and willingness to comply with all study procedures, including overnight polysomnography and follow-up
5. Ability to provide written informed consent

5.2 EXCLUSION CRITERIA

Participants will be excluded if any of the following criteria are met:

1. Known severe pulmonary disease (e.g., advanced chronic obstructive pulmonary disease) that, in the opinion of the investigator, may increase the risk of oxygen-induced hypercapnia

2. Unstable or clinically significant cardiopulmonary disease, including but not limited to decompensated heart failure, unstable angina, or clinically significant arrhythmia
3. Recent hospitalization (within the past 30 days) or anticipated need for hospitalization during the study period
4. Recreational or non-prescribed opioid use
5. Alcohol use exceeding 2 standard drinks per day or evidence of substance use disorder that may interfere with study participation
6. Presence of other sleep disorders or neurologic conditions that significantly affect breathing during sleep (e.g., neuromuscular disease), in the opinion of the investigator
7. Uncontrolled insomnia
8. Pregnancy or breastfeeding, or planning to become pregnant during the study period
9. Inability to tolerate study procedures, including overnight polysomnography
10. Inability to provide informed consent or comply with study procedures
11. Any medical, psychiatric, or social condition that, in the opinion of the investigator, would interfere with safe participation or interpretation of study results
12. Inability to safely participate in Comprehensive Opioid Management
13. Unstable or uncontrolled pain conditions
14. Recent significant changes in opioid regimen

5.3 LIFESTYLE CONSIDERATIONS

Participants will be instructed to maintain their usual daily routines, including diet, physical activity, and sleep schedules, throughout the study period. Participants will be asked to avoid initiating new medications or therapies that may affect sleep or respiratory function unless medically necessary.

Participants will be instructed to avoid alcohol consumption, recreational drug use, and excessive caffeine intake on the days of in-laboratory polysomnography (PSG) visits, as these substances may affect sleep architecture and respiratory parameters.

Any changes in medications, health status, or lifestyle factors that may affect sleep or breathing should be reported to the study team.

5.4 SCREEN FAILURES

Potential participants may undergo screening activities prior to informed consent to assess preliminary eligibility. Screening activities may include review of medical records, prior sleep studies, medication records, clinic notes, laboratory results, referral information, and responses to study questionnaires or REDCap screening surveys, in accordance with IRB approval and applicable HIPAA regulations, as described in Section 8.1 and DSMP Section 3.3 (Protections Against Risk).

Individuals determined to be ineligible prior to informed consent will be considered screen failures and will not be enrolled in the study.

Participants who provide informed consent but are subsequently found to be ineligible prior to randomization, or who are unable or unwilling to continue participation prior to randomization, will be classified as early discontinuations prior to randomization rather than screen failures. Reasons may include failure to meet eligibility criteria, withdrawal of consent, adverse events, safety concerns identified during study procedures, protocol-defined exclusion findings, or investigator determination that continued participation is not appropriate.

A minimal set of information may be retained for participants who consent but do not proceed to randomization in order to support study tracking, CONSORT reporting, safety oversight, and regulatory requirements. This information may include demographics, eligibility status, reason for discontinuation or non-randomization, and any adverse events (AEs) or serious adverse events (SAEs) occurring during the screening or pre-randomization period, consistent with DSMP Sections 4 and 6.

Participants who do not proceed to randomization will not undergo additional study procedures beyond those required for eligibility determination or participant safety. Re-screening may be permitted if the reason for ineligibility or discontinuation is temporary and has resolved, as determined by the investigator.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Participants will be randomized in a 1:1 ratio to either the Usual Care group or the Comprehensive Opioid Management group.

Participants randomized to the **Usual Care** group will continue opioid management with their existing treating clinician. Clinical management, including opioid prescribing, dose adjustments, and other pain-management decisions, will remain under the direction of the participant's treating clinician according to routine clinical practice.

Participants randomized to the Comprehensive Opioid Management group will be referred to the UC San Diego Opioid Management Program. Opioid management will be provided by the participant's treating clinician or designated opioid management provider using guideline-concordant clinical care. Treatment may include opioid dose adjustments, medication optimization, non-opioid pain therapies, behavioral interventions, and other pain-management strategies when clinically appropriate.

The research team will not prescribe opioids or direct opioid dose adjustments. All treatment decisions will remain under the authority of the participant's treating clinician or designated opioid management provider and will be based solely on clinical judgment rather than research requirements.

The distinction between the two randomized groups is the clinical pathway through which opioid management is provided rather than assignment to a protocol-mandated opioid taper or experimental opioid treatment.

Participants randomized to the Usual Care arm will continue opioid and pain management with their existing treating clinician, such as their primary care physician or pain specialist. Opioid prescribing, dose adjustments, medication changes, and other pain-management decisions will continue according to routine clinical practice. The research protocol does not require modification of the participant's opioid regimen.

Participants randomized to the Comprehensive Opioid Management arm will be referred to the UC San Diego Opioid Management Program and will receive the program's usual guideline-concordant clinical care. Management is individualized and may include opioid dose adjustments, medication optimization, non-opioid pain therapies, behavioral interventions, and other pain-management strategies when clinically appropriate. There is no protocol-specified tapering schedule, required opioid dose reduction, or study-directed prescribing.

Participants in both groups will undergo the same research assessments and follow-up schedule. The research team will collect safety and outcome data, including opioid exposure, sleep and respiratory measures, pain-related outcomes, and adverse events, but will not direct opioid prescribe or other clinical pain-management decisions.

Comparison of Study Groups

Usual Care	Comprehensive Opioid Management
Continue opioid management with the participant's treating clinician.	Referred to the UC San Diego Opioid Management Program.
Clinical management continues according to routine clinical care.	Clinical management follows the UC San Diego Opioid Management Program's usual guideline-concordant clinical care.
Opioid prescribing and dose adjustments remain at the discretion of the treating clinician.	Opioid prescribing, dose adjustments, medication optimization, and other pain-management strategies may be implemented when clinically appropriate by the treating clinician or designated opioid management provider.
No study-directed opioid management changes are required.	No study-directed opioid dose adjustments are required; all treatment decisions are based on clinical judgment.
Participants complete the same research assessments and follow-up schedule.	Participants complete the same research assessments and follow-up schedule.

6.1.2 DOSING AND ADMINISTRATION

Opioid dosing will be managed according to study arm assignment.

Participants randomized to the usual care arm will continue opioid therapy under the direction of their treating clinician. No protocol-directed dose adjustments will be required, and all prescribing decisions will remain the responsibility of the participant's usual care provider.

Participants randomized to the Comprehensive Opioid Management arm will undergo clinician-directed opioid management under the supervision of the UCSD Primary Care Opioid Management Program. Dose adjustments will be performed by the treating clinician (not the study team) and will be individualized based on participant safety, pain control, withdrawal symptoms, medication changes, and clinician judgment.

All opioid use, including dose changes and concomitant medications, will be documented throughout the study period.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Not applicable

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not applicable

6.2.3 PRODUCT STORAGE AND STABILITY

Not applicable

6.2.4 PREPARATION

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized in a 1:1 ratio to one of two study arms: usual care or referral to Comprehensive Opioid Management. Randomization will occur following completion of screening and baseline assessments.

The randomization schedule will be generated using a computer-based system, and allocation will be implemented using a secure method to ensure concealment prior to assignment.

Due to the nature of the intervention, this study will be conducted as an open-label trial. Participants and study clinicians will be aware of treatment assignment because clinical management strategies, including potential changes to opioid therapy, cannot be feasibly blinded.

To minimize bias, objective outcome measures will be used, including polysomnography-based assessments of ventilatory instability and sleep-disordered breathing. Standardized procedures will be used for data collection, scoring, and analysis.

Where feasible, outcome assessors (e.g., PSG scorers and data analysts) may be blinded to treatment assignment.

6.4 STUDY INTERVENTION COMPLIANCE

Study intervention compliance will be assessed based on adherence to the assigned study arm and participation in study procedures.

Participants randomized to the usual care arm will be considered compliant if they continue opioid management under the direction of their treating clinician and complete required study assessments and follow-up procedures.

Participants randomized to the Comprehensive Opioid Management arm will be considered compliant if they engage in the clinician-directed Comprehensive Opioid Management process and participate in recommended clinical follow-up and treatment management activities, as clinically appropriate. Because treatment plans and any opioid therapy modifications are individualized, strict adherence to a predefined treatment schedule is not required. Instead, compliance will be assessed based on participation in the Comprehensive Opioid Management process and ongoing clinical management.

Compliance will be monitored through participant self-report, opioid dose documentation, medical record review when available, twice weekly text-message safety check-ins, and twice-monthly telephone outreach, including evaluation of opioid use, medication changes, adverse events, withdrawal symptoms, pain control, mood symptoms including suicidality, respiratory symptoms, emergency care use, and study adherence.

Non-compliance will not automatically result in study discontinuation; however, persistent inability to participate in study procedures or assigned intervention may be evaluated on a case-by-case basis.

6.5 CONCOMITANT THERAPY

For this study, concomitant therapy includes all prescription medications, over-the-counter medications, supplements, and non-pharmacologic treatments used by the participant during the study period.

Participants will continue to receive standard clinical care throughout the study. Medications, including opioids and other therapies, will remain under the direction of the participant's treating clinician and/or opioid management provider.

Participants should avoid initiating new medications or making significant changes to existing medications that may affect respiratory function or sleep, including sedatives, benzodiazepines, and other

central nervous system depressants, unless medically necessary. All medication changes must be reported to the study team.

All concomitant medications and changes in therapy will be recorded in the case report forms (CRFs) at baseline and throughout the study, including during safety monitoring contacts and twice-monthly telephone outreach.

Concomitant therapies that may influence study outcomes, including medications affecting ventilatory control, sleep architecture, or opioid metabolism, will be documented and considered in data analysis. The potential impact of concomitant therapies on study endpoints will be assessed as part of the overall analysis plan.

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Criteria and procedures for discontinuation of study intervention are provided in DSMP §9.3 (Individual Participant Discontinuation and Withdrawal Criteria).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Criteria and procedures for participant discontinuation from the study and full withdrawal are provided in DSMP §9.3 (Individual Participant Discontinuation and Withdrawal Criteria).

7.3 LOST TO FOLLOW-UP

Criteria, contact-attempt sequence, documentation, and analytical handling of participants lost to follow-up are provided in DSMP §9.4 (Lost to Follow-Up).

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

This section describes study procedures and evaluations performed to assess the physiologic effects of clinician-directed Comprehensive Opioid Management on ventilatory stability and sleep-disordered

breathing in adults with chronic opioid use. The timing of study procedures is detailed in the Schedule of Activities (SoA), Section 1.3.

Screening Procedures

To determine preliminary eligibility, study personnel may review existing medical records, including prior sleep studies, medication records, clinic notes, laboratory results, and other relevant clinical information. Access to protected health information (PHI) for screening purposes will be conducted in accordance with institutional policy, IRB approval, and applicable HIPAA regulations. A partial waiver of HIPAA authorization may be used, as approved by the IRB, to permit review of records necessary to identify potentially eligible participants prior to obtaining informed consent.

Screening procedures will be conducted within 28 days prior to enrollment to determine participant eligibility.

Screening procedures will include:

- Review of inclusion and exclusion criteria
- Limited Medical and sleep history
- Limited Concomitant medication review
- Review of prior diagnostic sleep studies, if available

Baseline visit Procedures

A baseline visit will be performed, during which the following will be obtained:

- Informed consent
- Re-Review of inclusion and exclusion criteria
- Detailed Medical and sleep history
- Vitals and focused physical examination
- Detailed Concomitant medication review
- Questionnaires
- Blood draw

A baseline overnight polysomnography (PSG) will be performed if a qualifying PSG has not been completed within the prior 8 weeks or if there has been a clinically significant change in medical or sleep-related status.

Eligibility for further participation will be based on continued fulfillment of inclusion and exclusion criteria, including confirmation of sleep-disordered breathing (AHI3A $\geq$ 5 events/hour).

Randomization and Treatment Period

Participants assigned to the Comprehensive Opioid Management arm will receive individualized opioid and pain-management care under the supervision of the participant's treating clinician and/or the UCSD Opioid Management Program. Comprehensive Opioid Management will be conducted in accordance with clinical practice guidelines and may include changes to opioid therapy, medication management, and

other pain-management strategies, as clinically appropriate. Opioid prescribing decisions remain with the participant's treating or prescribing clinician or the UCSD Opioid Management Program. The research team does not prescribe opioids. Research contacts collect safety and outcome data and facilitate communication but do not direct opioid prescriptions or independently manage opioid therapy.

Participants randomized to the usual care arm will continue opioid management under the direction of their treating clinician and will not receive protocol-directed Comprehensive Opioid Management.

During the 26-week study period, participants will complete twice weekly text-message safety check-ins and twice-monthly telephone outreach. Telephone outreach may also occur in response to concerning, absent, or worsening text-check-in responses. Safety contacts will assess pain exacerbation, withdrawal symptoms, mood symptoms including suicidality, sedation, respiratory symptoms, emergency care use, medication changes, adherence to assigned follow-up, adverse events, and other safety concerns. Same-day PI review will occur when indicated according to DSMP escalation criteria.

12-Week Interim Assessment

At approximately Week 12, participants will complete an interim assessment conducted either remotely or in person. The visit will include review of medications, opioid use, medication changes, adverse events, and completion of study questionnaires. These assessments are intended to evaluate changes in clinical status and patient-reported outcomes during the study period. No overnight sleep study, blood collection, or psychomotor vigilance testing will be performed at this visit.

End-of-Study Assessments (Week 26 PSG)

At the end of the 26-week study period, participants will undergo a study visit including an overnight PSG, which serves as the primary endpoint assessment.

Assessments may include:

- Questionnaires and patient-reported outcomes
- Adherence review
- PSG: Sleep architecture, Respiratory events, including AHI, Oxygenation and gas exchange
- Morning Psychomotor Vigilance Test (PVT)
- Adverse event assessment
- Blood sampling/opioid level collection

Following overnight PSG visits, participants will undergo a standardized morning release assessment, including evaluation of alertness and fitness to drive, in accordance with DSMP Section 4.2.

In some circumstances, a study visit may need to be repeated if required study procedures cannot be completed, if a participant is unable to complete the visit, if technical or equipment issues occur, or if study data (e.g., overnight polysomnography recordings) are incomplete or of insufficient quality for analysis. Repeat visits are intended to ensure complete and evaluable study data whenever feasible.

Questionnaires and Patient-Reported Outcomes

All patient-reported outcome measures used in this study are validated instruments. No investigator-developed questionnaires will be used.

The patient-reported outcome (PRO) battery is harmonized with the NIH HEAL Initiative Common Data Elements (CDEs) for adult chronic pain research. The full battery and schedule of administration are described below; instrument-level recall windows are noted for transparency and interpretation of longitudinal follow-up assessments.

HEAL CDE core (adult chronic pain):

- Pain intensity and interference — PEG (3-item; past week).
- Physical functioning — PROMIS Physical Functioning Short Form 6b (current ability).
- Sleep — PROMIS Sleep Disturbance Short Form 6a (past 7 days).
- Pain catastrophizing — Pain Catastrophizing Scale Short Form (6-item or 13-item; situational).
- Depression — PHQ-9 (past 2 weeks).
- Anxiety — GAD-7 (past 2 weeks).
- Global satisfaction / impression of change — Patient Global Impression of Change (PGIC; change since baseline).
- Substance-use screener — TAPS-1 (past 12 months).
- Health-related quality of life — WHOQOL-BREF (past 2 weeks).

Sleep and fatigue adjuncts:

- PROMIS Sleep-Related Impairment Short Form 8a (past 7 days).
- PROMIS Fatigue Short Form 8a (past 7 days).
- Epworth Sleepiness Scale (ESS; usual lifestyle, trait measure).
- Pittsburgh Sleep Quality Index (PSQI, past month; includes the sleep-duration items).
- Insomnia Severity Index (ISI; past 2 weeks).

Opioid use, misuse, and safety screens:

- Current Opioid Misuse Measure (COMM; past 30 days).
- Subjective Opiate Withdrawal Scale (SOWS) monitored after randomization.
- Karolinska Sleepiness Scale (KSS) is administered the morning after every in-laboratory PSG before discharge, consistent with DSMP §4.2.

Prescription opioid quantification: Name of opioid, dose, prescription duration, total days exposed, and daily dose in morphine milligram equivalents (MME) will be captured for every prescribed opioid. MME calculations will use the NIH HEAL Morphine Milligram Equivalent Online Calculator (research-mme.wakehealth.edu), which provides evidence-based mapping factors for 29 opioids (traditional full agonists, partial agonists, and mixed-mechanism agents) and supports four standardized time-window calculation methods (Total Days Supply, On-therapy Days, Fixed Observation Window, and Maximum Daily Dose). For pre-specified analyses involving large datasets or offline use, the companion R package mmequiv (CRAN) will be used to replicate the same calculations. MME outputs are used for research characterization only and do not inform clinical prescribing. Citation: Adams MCB, Sward KA, Perkins ML, Hurley RW. Standardizing research methods for opioid dose comparison: the NIH HEAL morphine milligram equivalent calculator. PAIN. 2025;166(8) (doi:10.1097/j.pain.0000000000003529).

Collection Schedule: The full PRO battery will be collected at the baseline visit, at the interim visit, and at the end-of-study visit (Week 26). Safety monitoring assessments conducted during the treatment period

will evaluate opioid use, medication changes, withdrawal symptoms, pain control, mood symptoms including suicidality, respiratory symptoms, emergency care use, adverse events, and study adherence. Monitoring procedures, escalation criteria, and follow-up requirements are described in the study Data and Safety Monitoring Plan (DSMP).

Use of Existing Medical Data

Existing medical records and prior diagnostic studies may be used for screening and study data collection, as applicable. All data collection will comply with HIPAA regulations and institutional policies.

Qualified Personnel and Standardization

All study procedures, including PSG acquisition and scoring, physiologic monitoring, and neurobehavioral testing, will be performed by trained and qualified personnel using standardized procedures designed to minimize variability across study visits.

Biological Specimen Collection and Laboratory Evaluations

Blood samples will be collected at the Baseline and Week 26 visits by trained ACTRI research nurses using standard phlebotomy procedures. Approximately 10 mL of blood will be collected at each visit, for a total planned collection of approximately 20 mL over the course of the study. Samples will be used to measure opioid levels, characterize participant opioid exposure, and assess potential relationships between opioid use and study outcomes.Samples will be processed and analyzed using standard laboratory methods and institutional procedures. Where applicable, testing will be conducted in CLIA-compliant laboratories.

Serum opioid concentrations will be measured by multiplex liquid chromatography–tandem mass spectrometry (LC–MS/MS) overseen by Dr. Jeremiah Momper (UCSD Pharmacometrics and Analytical Chemistry Core).

8.2 SAFETY AND OTHER ASSESSMENTS

Participant safety will be monitored throughout the study by the Principal Investigator and study staff. Safety assessments will include review of adverse events, concomitant medications, opioid use, pain, withdrawal symptoms, mood symptoms (including suicidality), respiratory symptoms, emergency medical care use, medication changes, and other clinically significant changes in health status.

At baseline and the Week 26 end-of-study visit, participants will undergo overnight polysomnography (PSG). Following each overnight study, participants will complete a standardized morning release assessment to ensure they are safe for discharge.

Pregnancy Testing: Participants of childbearing potential will undergo a urine pregnancy test during the baseline visit before any study procedures are performed. Participants with a positive urine pregnancy test will not be enrolled. Additional urine pregnancy testing may be performed during study participation if pregnancy is suspected or clinically indicated.

During the 26-week treatment period, participants will receive twice-weekly text-message safety check-ins assessing pain exacerbation, withdrawal symptoms, mood symptoms (including suicidality), sedation, respiratory symptoms, emergency medical care use, medication changes, and adherence to assigned follow-up. Participants will also receive coordinator-administered telephone outreach at least twice monthly and as needed for any concerning, absent, or worsening text-message safety check-in response.

Participants reporting suicidal ideation, severe uncontrolled pain, suspected opioid withdrawal requiring urgent management, overdose concern, hospitalization, rapid functional decline, or other concerns indicating continued participation may be unsafe will receive same-day review by the Principal Investigator or designee. When appropriate, the participant's treating clinician or designated opioid management provider will be notified. All adverse events will be documented, reviewed, and managed according to the study Data and Safety Monitoring Plan.

Safety monitoring procedures, schedule of monitoring, escalation criteria, AE/SAE definitions, and reporting procedures are described in the study DSMP §4.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward or unfavorable medical occurrence in a participant that occurs during study participation, whether or not it is considered related to the research. An AE may include any new or worsening sign, symptom, abnormal laboratory finding, disease, injury, or psychological event that occurs after enrollment in the study. All adverse events will be documented, evaluated for severity and relationship to the study, followed until resolution or stabilization when appropriate, and reported in accordance with the study Data and Safety Monitoring Plan and applicable UC San Diego IRB requirements.
Definitions of adverse events (AEs), serious adverse events (SAEs), and unanticipated problems (UPs) are provided in the study Data and Safety Monitoring Plan (DSMP), Section 6.1, and will be applied throughout the study.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is any adverse event that occurs during study participation and results in any of the following: death, a life-threatening event, inpatient hospitalization or prolongation of an existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, or any other important medical event that, based on the judgment of the investigator, may jeopardize the participant's health or require medical or surgical intervention to prevent one of these outcomes. All serious adverse events will be reported and managed in accordance with the study Data and Safety Monitoring Plan, UC San Diego IRB requirements, and applicable sponsor reporting requirements.

Definitions of serious adverse events (SAEs) and unanticipated problems (UPs) are described in DSMP Section 6.1.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The severity of each adverse event will be assessed by the Principal Investigator or designee using the following categories:

- **Mild:** Awareness of signs or symptoms that are easily tolerated and do not interfere with usual daily activities.
- **Moderate:** Signs or symptoms that cause sufficient discomfort to interfere with usual daily activities.
- **Severe:** Signs or symptoms that prevent usual daily activities or result in significant clinical impairment. Severity refers to the intensity of an adverse event and does not necessarily indicate that the event is serious.

Adverse event severity will be graded using CTCAE v5.0 criteria as described in DSMP Section 6.2.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

The Principal Investigator or designee will assess the relationship of each adverse event to the study intervention using the following categories:

- **Not Related:** The adverse event is clearly due to factors unrelated to study participation.
- **Unlikely Related:** The adverse event has a temporal relationship to study participation but is more likely explained by the participant's underlying condition, concurrent illness, or other factors.
- **Possibly Related:** The adverse event has a reasonable temporal relationship to study participation and may be related, although other explanations are also possible.
- **Probably Related:** The adverse event has a reasonable temporal relationship to study participation, is unlikely to be explained by other factors, and is likely related to the study intervention or study procedures.
- **Definitely Related:** The adverse event is clearly related to the study intervention or study procedures and cannot reasonably be explained by other causes.

Assessment of relatedness between study procedures/interventions and adverse events will be performed according to the definitions and criteria described in DSMP Section 6.3.

8.3.3.3 EXPECTEDNESS

The Principal Investigator or designee will assess whether each adverse event is **expected** or **unexpected** based on the known risks described in the protocol, informed consent document, Investigator's Brochure (if applicable), and other relevant study documents.

- **Expected:** An adverse event that is consistent in nature, severity, and frequency with the known or anticipated risks of the study intervention or study procedures.
- **Unexpected:** An adverse event that is not consistent in nature, severity, or frequency with the known or anticipated risks of the study intervention or study procedures.

The expectedness assessment will be used to determine whether additional reporting to the UC San Diego Institutional Review Board (IRB), study sponsor, or other regulatory authorities is required in accordance with applicable policies and regulations.

Expectedness of adverse events will be determined by the Principal Investigator using the study protocol, DSMP, published literature, and known risks associated with study procedures and study interventions, as described in DSMP Sections 3 and 6

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events will be assessed from the time informed consent is obtained through completion of the participant's final study visit or early withdrawal from the study. Adverse events may be identified during scheduled study visits, twice-weekly text-message safety check-ins, twice-monthly telephone follow-up calls, review of study procedures, review of medical records when applicable, or through participant self-report.

Study staff will document all adverse events, including the onset date, severity, relationship to the study intervention or study procedures, actions taken, and outcome. Adverse events will be followed until resolution, stabilization, or until the participant completes study participation, as appropriate. Serious adverse events will be reported promptly and managed in accordance with the study Data and Safety Monitoring Plan, UC San Diego IRB requirements, and applicable sponsor reporting requirements.

Event assessment procedures, monitoring frequency, follow-up requirements, and reporting timelines are described in DSMP §§4 and 7

8.3.5 ADVERSE EVENT REPORTING

All adverse events will be documented by study staff and reviewed by the Principal Investigator or designee. The Principal Investigator will assess each adverse event for severity, relationship to the study intervention or study procedures, expectedness, and seriousness.

Serious adverse events will be reported to the study sponsor and the UC San Diego Institutional Review Board (IRB) in accordance with applicable federal regulations, institutional policies, and sponsor requirements. Any unanticipated problems involving risks to participants or others will also be reported promptly in accordance with UC San Diego IRB reporting requirements.

The Principal Investigator will oversee the review of all adverse events throughout the study and determine whether protocol modifications, additional participant monitoring, temporary suspension of study activities, or other corrective actions are necessary to protect participant safety. All adverse events will be summarized in study progress reports and the final study report, as applicable.

Adverse event (AE) reporting procedures and timelines are described in DSMP Section 7 and will be conducted in accordance with UCSD IRB, NHLBI, DSMB, and applicable regulatory requirements.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The Principal Investigator will review every AE — typically within one business day, and same-day for any event meeting red-flag criteria (Section 4.3.3) or potentially meeting SAE or unanticipated problem definitions — and will adjudicate final severity, expectedness, and relatedness classifications. Events meeting SAE or UP criteria will be reported to the IRB, NHLBI, and DSMB on the timelines specified in Section 7; all other AEs will be tabulated and reported to the DSMB at each scheduled review meeting and to the IRB at continuing review. Each event will be tracked longitudinally until resolution, stabilization, or determination that no further follow-up is feasible, and any new information altering the seriousness, expectedness, or relatedness assessment will trigger an updated report to the appropriate oversight bodies.

Event	Initial Timeline	Reported By	Reported To
Fatal or life-threatening unexpected suspected SAE	DSMB: within 24 hours; IRB and NHLBI: within 7 calendar days	PI or delegated investigator	DSMB, IRB, NHLBI
Non-fatal unexpected suspected SAE	Within 15 calendar days of initial receipt	PI or delegated investigator	IRB, DSMB, NHLBI
Unanticipated problem not an SAE	Within 10 working days of awareness	PI or delegated investigator	IRB, DSMB, NHLBI
All other AEs	DSMB: At scheduled DSMB review IRB: Annually at time of renewal	PI or delegated investigator	DSMB, IRB

Any IRB action involving suspension, termination, reportable noncompliance, major safety-related revision, or other determination materially affecting participant safety will be forwarded to NHLBI. Any protocol or consent amendment that may alter subject risk, monitoring intensity, study arms, stopping rules, or remote monitoring procedures will be submitted to the IRB and provided to NHLBI and the DSMB, as applicable, after IRB approval and before implementation unless necessary to eliminate immediate hazard.

FDA reportability: no IND or IDE is currently held for any aim of this study based on the current protocol; therefore no expedited FDA reporting is required. If a protocol change introduces an FDA-

regulated investigational use, the study will not proceed with that change until (i) an IND or IDE has been obtained, (ii) FDA expedited reporting timelines per 21 CFR 312.32 are incorporated into this DSMP, and (iii) the revised DSMP has been approved by the IRB and NHLBI.

Serious adverse event (SAE) reporting procedures, expedited reporting requirements, and oversight responsibilities are described in DSMP Section 7 and will be followed throughout the study.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants will be informed in a timely manner of any new information that may affect their willingness to continue participation in the study. If a serious adverse event, unanticipated problem, or other new safety information indicates that continued participation may place participants at increased risk, the Principal Investigator will determine whether participants should be notified, re-consented, withdrawn from the study, or referred for appropriate clinical evaluation or treatment.

When appropriate, revised informed consent documents reflecting new risk information will be submitted for UC San Diego Institutional Review Board (IRB) approval before being implemented, unless immediate action is necessary to eliminate an apparent hazard to participants.

8.3.8 EVENTS OF SPECIAL INTEREST

Events of special interest (ESIs) are clinically significant events that require prompt review by the Principal Investigator, regardless of whether they meet the criteria for a serious adverse event. ESIs for this study include:

- Opioid overdose or suspected overdose.
- Severe opioid withdrawal requiring urgent medical evaluation or treatment.
- Suicidal ideation, suicide attempt, or other significant psychiatric deterioration.
- Respiratory depression or other clinically significant respiratory events requiring emergency medical evaluation or hospitalization.
- Emergency department visits or hospitalizations related to pain management, opioid therapy, or respiratory complications.
- Newly identified severe sleep-disordered breathing requiring urgent clinical intervention.
- Any event that, in the judgment of the Principal Investigator, may place the participant at increased risk or warrant modification of study participation.

All ESIs will be reviewed promptly by the Principal Investigator or designee and managed in accordance with the study Data and Safety Monitoring Plan. Appropriate medical follow-up will be arranged, and reportable events will be submitted to the UC San Diego Institutional Review Board (IRB), study sponsor, and other regulatory authorities, as applicable.

Additional monitoring procedures, escalation criteria, PI review requirements, and reporting procedures are described in DSMP §§3.2, 4, 6, and 7.

8.3.9 REPORTING OF PREGNANCY

Pregnancy occurring during study participation will be reported to the Principal Investigator and managed in accordance with institutional policy and IRB requirements. Participants who become pregnant may be withdrawn from study intervention or additional study procedures if continued participation is not considered appropriate or safe, consistent with DSMP Section 9.3.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An unanticipated problem involving risks to participants or others is any incident, experience, or outcome that:

1. Is **unexpected** in nature, severity, or frequency given the research procedures described in the protocol, informed consent document, and other study materials;
2. Is **related or possibly related** to participation in the research; and
3. Suggests that the research places participants or others at a **greater risk of harm**, including physical, psychological, economic, or social harm, than was previously known or recognized.

The Principal Investigator or designee will evaluate all adverse events and other reportable events to determine whether they meet the criteria for an unanticipated problem involving risks to participants or others. Any unanticipated problems will be reported in accordance with the study Data and Safety Monitoring Plan, UC San Diego Institutional Review Board (IRB) requirements, sponsor requirements, and applicable federal regulations.

Definitions of unanticipated problems (UPs) are described in DSMP Section 6.1 and will be applied throughout the study.

8.4.2 UNANTICIPATED PROBLEM REPORTING

All unanticipated problems involving risks to participants or others will be reported immediately to the Principal Investigator upon awareness by study personnel. The Principal Investigator or designee will evaluate each event to determine whether it meets the criteria for an unanticipated problem and whether any immediate actions are necessary to protect participant safety.

Reportable unanticipated problems will be submitted to the UC San Diego Institutional Review Board (IRB), the study sponsor, and other regulatory authorities, as applicable, in accordance with federal regulations, institutional policies, sponsor requirements, and the study Data and Safety Monitoring Plan.

The Principal Investigator will determine whether corrective actions, including protocol modifications, revisions to the informed consent document, additional participant monitoring, temporary suspension of study activities, or other measures, are necessary to minimize risk to participants. Participants will be informed of any new information that may affect their willingness to continue participation in the study, as appropriate.

Unanticipated problem (UP) reporting procedures and timelines are described in DSMP Section 7 and will be conducted in accordance with UCSD IRB, NHLBI, DSMB, and applicable regulatory requirements.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed in a timely manner of any unanticipated problem involving risks to participants or others that may affect their willingness to continue participation in the study. The Principal Investigator will determine whether participants should be notified, re-consented using an Institutional Review Board (IRB)-approved revised informed consent document, withdrawn from the study, or referred for appropriate clinical evaluation or treatment.

When appropriate, revised informed consent documents reflecting new risk information will be submitted for UC San Diego Institutional Review Board (IRB) approval before implementation, unless immediate action is necessary to eliminate an apparent hazard to participants.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary hypothesis is that guideline-concordant, clinician-directed Comprehensive Opioid Management will improve ventilatory stability compared with usual care in adults with chronic opioid use and sleep-disordered breathing.

The null hypothesis (H0) is that there is no difference in ventilatory stability between participants receiving Comprehensive Opioid Management and those receiving usual care.

The alternative hypothesis (H1) is that participants receiving Comprehensive Opioid Management will demonstrate improved ventilatory stability compared with those receiving usual care.

Secondary hypotheses are that Comprehensive Opioid Management will be associated with improvements in sleep-disordered breathing severity, gas exchange, neurobehavioral performance, patient-reported outcomes, pain-related outcomes, and opioid exposure compared with usual care.

9.2 SAMPLE SIZE DETERMINATION

The sample size for this study will be based on the parent grant statistical plan. This study is designed as a randomized, controlled, parallel-group study comparing Comprehensive Opioid Management with usual care over approximately 26 weeks in adults with chronic opioid use and sleep-disordered breathing.

The planned sample size is intended to provide adequate power to evaluate differences between groups in ventilatory stability and sleep-disordered breathing physiology from baseline to the Week 26 end-of-study assessment.

Participants who complete baseline and Week 26 polysomnography will be considered evaluable for the primary efficacy analysis. Additional participants may be enrolled to account for anticipated attrition, withdrawal, incomplete PSG data, or inability to complete the 26-week follow-up period.

The final sample size and power assumptions will be confirmed with the study statistician and parent grant statistical analysis plan.

9.3 POPULATIONS FOR ANALYSES

Intent-to-Treat (ITT) Population
The intent-to-treat population will include all participants who are randomized, regardless of adherence to the assigned intervention or completion of study procedures. Participants will be analyzed according to their randomized study arm (usual care or Comprehensive Opioid Management). Per-Protocol (PP) Population
The per-protocol population will include participants who complete the study without major protocol deviations that could affect the primary outcome. This includes participants who complete both baseline and end-of-study (Week 26) polysomnography (PSG) and who reasonably adhere to their assigned study arm.

Safety Population
The safety population will include all participants who are randomized and have at least one post-baseline safety assessment. Safety analyses will be conducted according to the treatment actually received, when applicable.

Efficacy Population
The efficacy population will include participants with evaluable baseline and end-of-study (Week 26) PSG data. This population will be used for primary and secondary efficacy analyses.

Handling of Missing Data
Participants with missing outcome data, including incomplete PSG assessments, will be included in the ITT population. The handling of missing data will be specified in the statistical analysis plan.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics:

- Continuous variables: mean ± standard deviation or median (IQR)
- Categorical variables: counts and percentages

Inferential testing:

- Two-sided tests
- Significance level: $p < 0.05$
- 95% confidence intervals

Analyses will account for the randomized parallel-group design and repeated measures over time, as applicable. A formal Statistical Analysis Plan (SAP) will be finalized prior to database lock and unblinding.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint will be analyzed by comparing the change from baseline to the end-of-study assessment (Week 26) between the Comprehensive Opioid Management
group and the usual care group.

Analyses will be conducted using appropriate statistical methods for a parallel-group design. The primary comparison will evaluate between-group differences in ventilatory stability.

Results will be presented as:
• Estimated mean differences between groups
• 95% confidence intervals

Analyses may adjust for baseline values of the outcome measure, as appropriate.

Missing data will be handled using appropriate statistical methods, as specified in the statistical analysis plan (SAP).

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will be analyzed to evaluate the effects of guideline-concordant, clinician-directed Comprehensive Opioid Management compared with usual care on sleep-disordered breathing, gas exchange, neurobehavioral performance, patient-reported outcomes, pain-related outcomes, and opioid exposure.

Analyses will compare changes from baseline to the end-of-study assessment (Week 26) between the two study groups using appropriate statistical methods for a parallel-group design.

Continuous outcomes (e.g., AHI, transcutaneous carbon dioxide [$TcCO_2$], and neurobehavioral performance measures) will be summarized using descriptive statistics and analyzed using appropriate parametric or nonparametric methods, as specified in the statistical analysis plan (SAP).

Categorical outcomes will be summarized using counts and percentages and compared between groups using appropriate statistical tests.

Results will be presented as estimated between-group differences with corresponding 95% confidence intervals, as applicable.

Adjustment for baseline values and other covariates may be performed, as specified in the SAP.

Multiplicity adjustment for secondary endpoints will be addressed in the SAP, if applicable.

9.4.4 SAFETY ANALYSES

Safety analyses will be conducted to evaluate the safety and tolerability of guideline-concordant, clinician-directed Comprehensive Opioid Management compared with usual care over the 26-week study period.

Safety analyses will be performed using the safety population, defined as all participants who are randomized and have at least one post-baseline safety assessment. Analyses will be conducted according to the treatment received, when applicable.

Adverse events (AEs) and serious adverse events (SAEs) will be summarized by treatment group using descriptive statistics, including the number and percentage of participants experiencing events. Events will be categorized by severity and relationship to study intervention.

Additional safety assessments will include evaluation of opioid use, dose changes, withdrawal symptoms, pain control, and clinically significant changes in health status. These outcomes will be summarized descriptively over the study period.

No formal hypothesis testing is planned for safety endpoints unless specified in the statistical analysis plan (SAP).

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics will be summarized for all randomized participants and presented by treatment group (usual care and Comprehensive Opioid Management).

Descriptive statistics will be used to summarize demographic and clinical variables collected at baseline, including age, sex, body mass index (BMI), medical history, opioid use and dosing, and baseline sleep-disordered breathing measures.

Continuous variables will be summarized using means, standard deviations, medians, and ranges, as appropriate. Categorical variables will be summarized using counts and percentages.

Baseline characteristics will be reviewed to assess comparability between treatment groups. No formal statistical testing is planned for baseline comparisons unless specified in the statistical analysis plan (SAP).

9.4.6 PLANNED INTERIM ANALYSES

No formal interim analyses of efficacy are planned.

Safety data will be monitored on an ongoing basis throughout the study period, including review of adverse events, serious adverse events, opioid use, withdrawal symptoms, and pain control, in accordance with the data safety monitoring plan.

Any additional interim analyses, if deemed necessary, will be conducted in accordance with the statistical analysis plan (SAP) and applicable regulatory and institutional requirements.

9.4.7 SUB-GROUP ANALYSES

Subgroup analyses may be conducted to explore whether the effects of guideline-concordant, clinician-directed Comprehensive Opioid Management on ventilatory stability and related outcomes vary across participant characteristics.

Potential subgroups may include baseline opioid dose, baseline sleep-disordered breathing severity, demographic factors (e.g., age, sex), and other clinically relevant variables.

Subgroup analyses will be considered exploratory in nature and may not be powered to detect statistically significant differences. Results will be interpreted with caution.

Details regarding subgroup definitions and analytical methods will be specified in the statistical analysis plan (SAP).

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be recorded in case report forms (CRFs) and maintained in the study database in accordance with institutional policies and applicable regulatory requirements.

Data collected will include demographic information, medical history, opioid use and dosing, polysomnography (PSG) measures, physiologic assessments, neurobehavioral testing, patient-reported outcomes, and safety data, including adverse events and concomitant medications.
Individual participant data will be available for review, as appropriate, for purposes of data monitoring, quality assurance, and regulatory compliance. Data listings may be generated to support statistical analyses, safety reviews, and study reporting.

All data will be handled in accordance with applicable privacy and confidentiality regulations, including HIPAA, and will be stored securely with access limited to authorized study personnel.

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses may be conducted to further evaluate the relationships between opioid exposure, ventilatory control, and sleep-disordered breathing outcomes.

These analyses may include assessment of associations between changes in opioid dose and changes in physiologic measures, including ventilatory instability, sleep-disordered breathing severity, gas exchange, and related outcomes.

Additional exploratory analyses may examine relationships between baseline characteristics, opioid use patterns, and study outcomes to identify potential predictors of response to Comprehensive Opioid Management.

Exploratory analyses will be considered hypothesis-generating and will not be adjusted for multiple comparisons. Results will be interpreted with caution.

Details regarding exploratory analyses will be specified in the statistical analysis plan (SAP).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

The study may be discontinued prematurely by the Principal Investigator, sponsor/funding agency, DSMB, Institutional Review Board (IRB), or other regulatory authorities for reasons including, but not limited to:

- Participant safety concerns
- Insufficient participant enrollment
- New scientific information affecting the risk-benefit assessment
- Protocol noncompliance
- Loss of funding or administrative reasons
- Determination that continuation of the study is no longer scientifically or ethically appropriate

If the study is terminated or closed early, enrolled participants will be informed as appropriate, and procedures for participant safety and follow-up will be conducted at the discretion of the investigator.

Study records and data will be maintained in accordance with institutional policies, IRB requirements, sponsor requirements, and applicable regulatory guidelines.

The study will be considered complete when all participants have completed study procedures, required follow-up, and data collection activities, and all regulatory and data management activities have been finalized.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, study monitors, and authorized regulatory representatives. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants.

Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or authorized regulatory representatives or study monitors may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at REDCap. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by REDCap research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at REDCap.

Certificate of Confidentiality (if applicable)

To further protect the privacy of study participants, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Blood samples collected for opioid level measurement will be used for the purposes outlined in this study protocol. With participant consent, specimens and data may be stored for future research related to sleep-disordered breathing, ventilatory control, and opioid physiology.

Stored specimens and data will be coded with a unique subject identifier, and other identifying information will be removed. Access to stored materials will be limited to authorized investigators and governed by institutional policies.

Participants will have the option to decline future use of their specimens and data as part of the informed consent process.

No genetic testing is planned as part of this study.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

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In addition, study oversight will be provided by an NIH-appointed independent Data and Safety Monitoring Board (DSMB). The DSMB includes individuals with expertise in sleep disorders, cardiopulmonary disease, clinical trials, biostatistics, and medical ethics. The DSMB will review safety data and study conduct at regular intervals and provide recommendations to the Principal Investigator. DSMB membership will be finalized by the NIH.

10.1.5 SAFETY OVERSIGHT

Safety oversight will be conducted in accordance with the separately submitted Data and Safety Monitoring Plan.

The Principal Investigator (PI) will oversee participant safety throughout the study, including review of adverse events (AEs), serious adverse events (SAEs), clinically significant findings, protocol deviations, and participant safety concerns, as described in DSMP Sections 4, 6, and 7.

An independent Data and Safety Monitoring Board (DSMB) will provide additional oversight and will review study conduct, participant safety, adverse events, and protocol compliance at regular intervals, as described in DSMP Sections 5 and 7.

Safety monitoring procedures, escalation criteria, and reporting requirements for adverse events, serious adverse events, and unanticipated problems are described in DSMP Sections 6 and 7 and will be conducted in accordance with UCSD IRB, NHLBI, DSMB, and applicable regulatory requirements.

10.1.6 CLINICAL MONITORING

Clinical monitoring will be conducted to ensure participant safety, protocol compliance, data integrity, and adherence to applicable regulatory requirements, institutional policies, Good Clinical Practice (GCP), and the study DSMP.

We will make every effort to maintain patient privacy and confidentiality both during and following the study. Electronic study data will be de-identified by substitution of codes for names and hospital identifiers and will be stored on a secure disk for access by Investigator and study staff only and any hard copies will be stored in a locked cabinet. In all correspondence and in internal study reports that require identification of individual subjects, subjects will be referred to and known by their ID number and character name code. All subject data forms (CRF's) will only list the ID number. All research staff are CITI certified and have had impressed upon them the importance of confidentiality. Data will be stored only at UCSD sites and its use will be confined to that specified in this protocol and its approved amendments. The PI will be responsible for reviewing databases and regulatory material regularly to ensure that we are in good compliance.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of trained study personnel under the supervision of the Principal Investigator.

Study data will be entered into REDCap, a secure, 21 CFR Part 11- ready electronic data capture system. The system includes password protection and internal quality checks to identify incomplete or inconsistent data.

Source documents will be maintained for all participants, and data entered into the electronic system will be verified against source documentation.

Access to study data will be restricted to authorized personnel. The Principal Investigator is responsible for ensuring the accuracy, completeness, and timeliness of all data collected.

10.1.7.2 STUDY RECORDS RETENTION

Study records will be retained in accordance with institutional and regulatory requirements.

All study documents will be maintained for a minimum of three (3) years following submission of the final study report or longer if required by applicable regulations or sponsor requirements.

No study records will be destroyed without appropriate authorization.

10.1.8 PROTOCOL DEVIATIONS

Protocol deviations will be documented, reviewed, and managed in accordance with study procedures and applicable regulatory requirements. Additional monitoring, quality control, escalation, and reporting procedures are described in DSMP §§4, 5, and 7.

10.2 ADDITIONAL CONSIDERATIONS

No additional considerations are identified at this time.

10.3 ABBREVIATIONS

AE — Adverse Event
AHI — Apnea–Hypopnea Index
AHIflow — Apnea–Hypopnea Index based on airflow
ANCOVA — Analysis of Covariance
BMI — Body Mass Index
CFR — Code of Federal Regulations
CLIA — Clinical Laboratory Improvement Amendments
CMP — Clinical Monitoring Plan
COC — Certificate of Confidentiality
CONSORT — Consolidated Standards of Reporting Trials
CRF — Case Report Form
DHHS — Department of Health and Human Services
DSMB — Data and Safety Monitoring Board
eCRF — Electronic Case Report Form
ESS — Epworth Sleepiness Scale
FDA — Food and Drug Administration
FDAAA — Food and Drug Administration Amendments Act of 2007
FFR — Federal Financial Report
GCP — Good Clinical Practice
GLP — Good Laboratory Practice
GMP — Good Manufacturing Practice
HIPAA — Health Insurance Portability and Accountability Act
ICH — International Council for Harmonisation
ICMJE — International Committee of Medical Journal Editors
IRB — Institutional Review Board
ITT — Intention-to-Treat
LSMEANS — Least-Squares Means
MedDRA — Medical Dictionary for Regulatory Activities
MOP — Manual of Procedures
NCT — ClinicalTrials.gov Identifier
NIH — National Institutes of Health
NIH IC — National Institutes of Health Institute or Center
OHRP — Office for Human Research Protections
PI — Principal Investigator
PSG — Polysomnography
PVT — Psychomotor Vigilance Test
QA — Quality Assurance
QC — Quality Control
REDCap — Research Electronic Data Capture (secure web-based application for data collection)
SAE — Serious Adverse Event
SAP — Statistical Analysis Plan

SOA — Schedule of Activities
SOC — System Organ Class
SpO_2 — Peripheral Oxygen Saturation
SOP — Standard Operating Procedure
$TcCO_2$ — Transcutaneous Carbon Dioxide
UP — Unanticipated Problem
US — United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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