Comparative Effectiveness of Zolpidem/Trazodone and Cognitive Behavioral Therapy for Insomnia in Rural Adults (COZI)

Study Protocol

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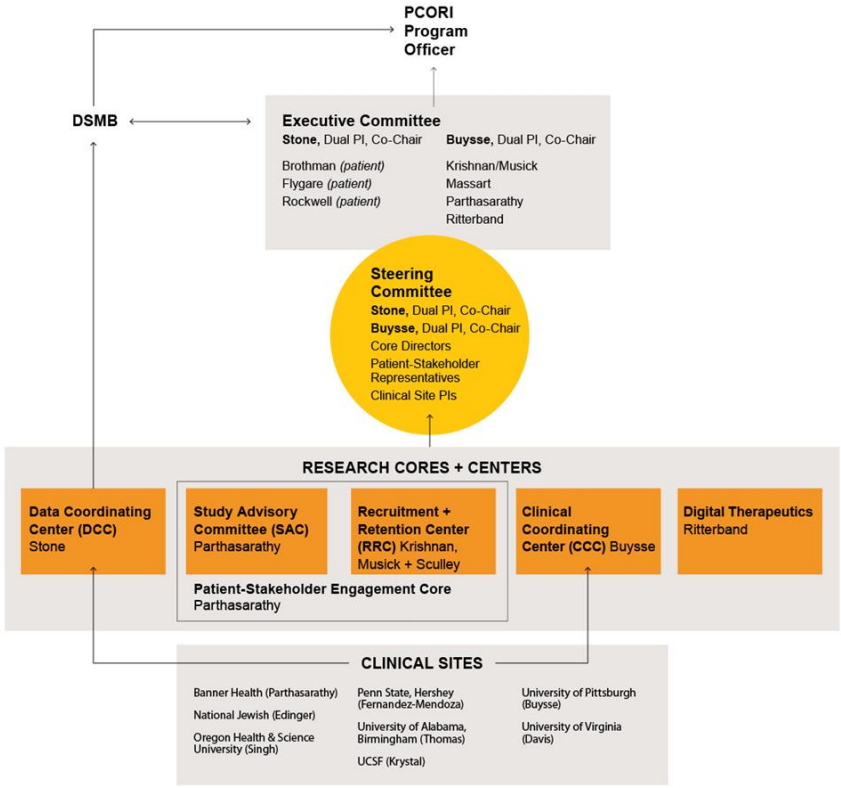
PROJECT SUMMARY

COZI is a randomized, 3-arm, parallel-group, multi-site comparative effectiveness trial of three treatment strategies for chronic insomnia. Participants are adults living in rural communities, recruited from their primary care provider's practice. Participants will be randomized to one of 3 treatment arms to compare effectiveness and safety: 1) medication (zolpidem or trazodone); 2) CBT-I (Cognitive-Behavioral Therapy for Insomnia) using the online SHUTi (Sleep Healthy Using the Internet) program; or 3) combination treatment with medication + CBT-I . Outcomes will be assessed immediately post-treatment (9 weeks), and at 6 and 12-month follow-up.

COZI will recruit and study 1200 patients across 8 hub sites (150 per site), each of which will collaborate with affiliated primary care practices. Recruitment methods may vary by hub and practice, according to site-specific resources. Recruitment methods will include traditional methods (posters, brochures, etc.) as well as electronic health record (EHR)-based recruitment where supported; all participants must be referred by a primary care practitioner. Referrals will be transmitted to the research team at the affiliated hub, who will complete telephone or online screening and voluntary informed consent. Eligible patients will complete baseline evaluations online, then be randomized to one of three interventions: Medication, Medication + CBT-I , or CBT-I , in a 1:1:1 ratio. Pre-treatment baseline and follow-up research assessments and other research procedures will be completed online in the participant's home. For participants randomized to a medication arm, the medication will be prescribed and monitored by their primary care provider, following published treatment guideline, as would be done in "usual practice." Participants randomized to CBT-I will be instructed on how to complete the online self-guided CBT-I intervention. All participants will complete follow-up assessments at 9 weeks, 6, and 12 months.

PROJECT MANAGEMENT



COZI is guided by a **Steering Committee**, with input from PCORI, the DSMB, and the Research Cores and Centers. The Steering Committee comprises the Dual PIs, Core Directors, two patient-stakeholder representatives, and two clinical hub site PIs.

The project team is led by Dual PIs Stone (Contact PI) and Buysse. Research Cores and Centers include the **Data Coordinating Center** at CPMC (Stone); the **Clinical Coordinating Center** (CCC) at Pitt (Buysse); the **Digital Therapeutics Core** at University of Virginia (Ritterband); and the **Patient-Stakeholder Engagement Core** (PSEC) at the University of Arizona (Parthasarathy). The PSEC comprises a **Study Advisory Committee** (SAC) and the **Recruitment and Retention Center** (RRC) at the University of Illinois Chicago (Krishnan, Musick, Sculley). The eight **clinical hub sites** are each led by a PI with expertise in insomnia clinical trials, and a Co-I from primary care practice. Two site leads serve on the Steering Committee to provide input into site-level operations and recruitment/retention plans.

Overview of Leadership and Organizational Structure

The Steering Committee (SC) is the main decision-making body of the study. It includes members of the EC, 8 site leads, and the study statistician. The SC convenes monthly via teleconference to review progress on major milestones, guide decision-making for execution by the EC, and approve the protocol (initially, and subsequent modifications). In addition, the SC will meet once per year in person (or virtual depending on status of pandemic) in tandem with SAC meetings in Chicago, Illinois or Tucson, Arizona.

The Executive Committee (EC) is responsible for executing the decisions made by the Study Advisory Committee (SAC), and communicating with outside entities including the Data and Safety Monitoring Board (DSMB) and PCORI. The EC includes the Lead PIs (Stone and Buysse), the Lead Patients (Brothman, Rockwell), Patient Advocacy Lead (Flygare), each of the core/sub-core leads and Co-Is (Parthasarathy, Krishnan, Erwin and Ritterband), the primary care Co-I (Massart) and the Data Coordinating Center Project Director. The EC will meet weekly-biweekly in Year 1 to review progress towards milestones, review preliminary data, troubleshoot challenges, and coordinate operations. Thereafter (Years 2-4) the EC will continue to meet twice per month. We will increase the frequency of meetings as needed.

Study Advisory Committee (SAC). The SAC is the main source of study input from 8 key stakeholder groups: patients, patient advocacy, providers, purchasers, payors, product makers, policymakers and investigator/ scientists. The SAC will communicate with the EC on issues pertaining to study design and feasibility, recruitment methods and procedures, finalization of study outcomes, procedures for study implementation, monitoring study progress, and dissemination of findings to communities of interest. The SAC will meet two times per year, once via teleconference, and once in person.

Hub Advisory Committee (HAC). The HAC will convene biweekly in Year 1 and biweekly-monthly in Years 2-4. The HAC is led by the RRC PIs. Its mission is to develop, modify, and disseminate best practices for recruitment and retention of primary care practices and study participants. The HAC serves as a vehicle for hub sites to share best practices and seek input on recruitment challenges.

In-Person Project Meetings. We held a *kick-off meeting* in year 1 that convened the Steering Committee and Study Advisory Committee. At the end of year 4, we will reconvene this group for a *dissemination meetin*g to discuss preliminary study findings and decide on plans for publication and other dissemination strategies such as press releases and media.

Katie L. Stone, PhD (Prime PI, Director of the Data Coordinating Center [DCC])

Daniel J. Buysse, MD (Dual PI, Director of the Clinical Coordinating Center [CCC])

Sairam Parthasarathy, MD (Co-I, Director of the Patient and Stakeholder Engagement Core[PSEC]),

Lee Ritterband, PhD (Co-I, Director of the Digital Therapeutics Core)

Jerry A. Krishnan, MD, PhD (Co-I, Director of the Recruitment and Retention Center [RRC], a component of the PSEC)

Arthur Brothman, PhD (patient investigator and consultant to the PSEC)
Heather Rockwell, MPW (patient member of SAC and SC)

Julie Flygare, JD (patient advocate and member of the PSEC)

Eric Vittinghoff, PhD (Statistician), is Professor of Biostatistics at UCSF

Mylynda Massart, MD, PhD (Co-I at Pitt/UPMC) is a practicing family physician

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RATIONALE AND BACKGROUND INFORMATION

Insomnia is a prevalent health condition with important consequences. By its very definition, chronic insomnia disorder (CID) is a patient-centered problem: Dissatisfaction with the quality or quantity of nighttime sleep, marked by difficulty falling asleep, maintaining sleep, or early awakening. Additional criteria include distress or impaired function, adequate sleep opportunity, frequency $\geq$3 nights/week, and duration $\geq$3 months. The prevalence of insomnia *symptoms* in adults is ~20-30%, and the prevalence of CID ~5-10%. Symptoms persist for $\geq$3 years in 40% of patients. Insomnia occurs in 10-26% of primary care patients. It is comorbid with, and associated with increased risk for, depression, obesity, hypertension, falls, cognitive decline and mortality. Chronic insomnia leads to reduced quality of life, lost work productivity through both presenteeism and absenteeism, and increased health care costs. Insomnia disproportionally affects the elderly, women, socio-economically disadvantaged, and racial/ethnic minorities. Despite its prevalence and serious consequences, individuals with insomnia often feel isolated and misunderstood by family members, co-workers, and providers. Patients are specifically dissatisfied with health care professionals' lack of treatment knowledge beyond "sleep hygiene" and medications. CID is a common and consequential health condition, but patients' distress and treatment needs are poorly addressed.

FDA-approved medications include benzodiazepines (e.g., temazepam, triazolam), benzodiazepine receptor agonists (BzRA, e.g., zolpidem, eszopiclone) orexin receptor antagonists (e.g., suvorexant), melatonin receptor agonists (e.g., ramelteon), and doxepin. Data from the National Health and Nutrition Epidemiological Survey 1999-2010 showed that 19.2% of adults took at least one sleep aid in the prior month. Zolpidem is the most commonly prescribed FDA-approved drug for insomnia, accounting for 62% of the 18.5 million prescriptions for hypnotics in 2011. Prescriptions for BzRAs have increased since 2004, driven by long-term prescriptions in primary care, and underscoring the need for long-term studies of their benefits

and harms. The efficacy of hypnotic medications is supported almost exclusively by industry-sponsored studies, most of which compare a single medication to placebo, and none of which have compared zolpidem to CBT-I. Although individual studies for specific hypnotics have large sample sizes, the number of trials per agent is small, the magnitude of effects modest, the outcomes focused on sleep measured using polysomnography rather than patient-reported outcomes (PROs), and the duration of treatment short (4-12 weeks). Meta-analyses support the short-term efficacy of benzodiazepines and BzRA. A recent Clinical Practice Guideline found weak evidence for the use of FDA-approved hypnotics, and weak evidence against other agents, including trazodone, diphenhydramine, and melatonin. In particular, zolpidem is efficacious for self-report and objective measures, in both adults and older adults. One longer-term study has demonstrated the efficacy of nightly zolpidem over 6 months. This evidence supports our choice of zolpidem as one of the medication treatments. Nevertheless, data from a survey of providers we collected suggest that many providers are reluctant to prescribe zolpidem because of its DEA Schedule IV designation, the risk for physiological dependence, the risk for other side effects such as complex sleep-related behaviors, and concerns about co-prescription with other controlled drugs. **Trazodone** is a sedating drug that is FDA-approved for treatment of depression, but is increasingly used at low doses off-label for the treatment of insomnia. Our survey results suggest that many providers perceive it to be safer and less likely to produce physiological dependence or other side effects than zolpidem. Moreover, a recently published article in JAMA (on which Dual PI Buysse was an author) utilized an analysis of IBM Marketscan Research Databases to examine prescribing trends for zolpidem and low-dose trazodone (typical doses prescribed for insomnia) in the United States over the period 2011 through 2018. Prescriptions for trazodone increased significantly and prescriptions for zolpidem decreased significantly over this time interval. In particular, the percentage of adults prescribed trazodone (< 150mg/day) increased from 1.25% to 1.82%, whereas the percentage prescribed zolpidem decreased from 4.56% to 2.50%. Similar trends were observed for patients with listed insomnia diagnoses. Of note, while zolpidem remains somewhat more commonly prescribed than trazodone, the gap is clearly closing.

Despite being used commonly for the treatment of chronic insomnia, there is limited evidence of the effectiveness of trazodone for this purpose. The only randomized, placebo-controlled trial in adults with primary insomnia compared 1-week and 2-week changes in self-reported sleep latency and duration, and sleep quality among 278 patients randomized to zolpidem (10mg), trazodone (50mg) or placebo. At the two-week follow-up, neither medication performed significantly better than controls for sleep quality; inspection of the data suggest stable effects of the two active medications, and increasing effect of placebo over this interval. A 2018 meta-analysis identified 7 randomized placebo-controlled trials of trazodone for treatment of insomnia with a total sample size of 4295. Overall findings of the meta-analysis indicated no improvements in sleep efficiency, sleep latency, or sleep duration, but patients randomized to trazodone did perceive significantly better subjective sleep quality based on 3 of the studies that collected this outcome (standard mean difference= -0.41; 95% confidence interval -0.82 - -0.0; p=.05). Of note, only one of these 3 studies with sleep quality outcomes was conducted in adults with primary insomnia, and this study found no significant effects.

Thus, data supporting the efficacy and safety of trazodone for insomnia is much more limited than is the case for zolpidem. There has never been a large, placebo-controlled trial to assess the efficacy and safety of trazodone for chronic insomnia. **Extensive discussion of these two medication options within the COZI Steering, Executive and Hub Advisory Committees leaves us in equipoise about which would be the better medication option for a comparative effectiveness trial with CBT-I, which professional organizations recommend as the first line treatment for insomnia. This state of**

equipoise had led us to a stakeholder-guided modification to the COZI study: using patient-provider medication choice of zolpidem or trazodone for patients in the two medication conditions.

CBT-I is a multicomponent therapy including education, stimulus control instruction, sleep restriction, and cognitive restructuring. CBT-I is typically administered over 6-8 individual sessions by a therapist, with self-monitoring and behavioral/cognitive homework between sessions. Meta-analyses and standards of practice papers support the efficacy of CBT-I vs. active and inactive comparators. Although most trials have included small numbers of participants, effects on self-report measures are robust, with smaller improvements on actigraphy and polysomnography. Efficacy is maintained over 6-12 months. CBT-I is also efficacious among individuals with comorbid conditions. CBT-I dissemination is limited by the number of therapists and inconsistent insurance coverage. Consequently, CBT-I has been adapted to include briefer treatments and self-guided Internet versions, including Sleep Healthy Using the Internet (SHUTi) and Sleepio. Internet CBT-I has broad accessibility, consistent treatment fidelity, comparable efficacy to standard CBT-I, and sustained effects over 1 year. SHUTi is supported by multiple RCTs, with robust data for acceptance, efficacy, and adherence. This evidence supports our choice of CBT-I (SHUTi) as the treatment comparator.

Critical evidence gaps remain. The extant intervention evidence fails to address the most important questions to patients and clinicians: Which treatment is best in terms of benefits and harms? Is combined treatment better than medication or CBT-I alone? Which treatment is best for me? Published clinical guidelines for the treatment of CID support CBT-I, hypnotics, or combination treatment, but they also call for long-term studies comparing effectiveness, adherence, and harms of these efficacious treatments. Our study directly addresses these critical evidence gaps.

Previous studies comparing medication, CBT-I, and combination treatment have included small samples (<80) of highly- selected participants at single research sites, inadequately powered for examining differences in treatment response . No “real-world” pragmatic clinical effectiveness trials have been conducted. Previous studies suggest faster response to medications, but better short and long-term (12-24 months) outcomes with CBT-I. The evidence base on combination treatment is even more limited, but suggests more enduring effects than medication alone, better response and remission rates with initial combined treatment(78), and lower zolpidem use. While instructive, these studies offer no definitive conclusions regarding comparative effectiveness of treatments for CID.

Patient preferences favor behavioral over pharmacologic treatments on the basis of acceptability, expectation of overall benefits, effects on daytime function, and side effects. However, the treatments are expected to be equally efficacious, and treatment acceptability does not correlate with outcomes. Obstacles to CBT-I include limited awareness among providers, few service providers, and higher initial cost due to a lack of insurance coverage(81). Primary care providers believe their patients rely too heavily on medications, but lack resources to direct patients to CBT-I. Our own preliminary data (see below) further highlight the equipoise experienced by patients and providers. In their own ways, patients and providers identify the same knowledge gaps revealed by currently-available evidence.

These evidence gaps are uniquely relevant to rural healthcare settings. There is no single definition for “rural”. One example is the US Department of Agriculture, which bases its definition on county-level data. “Nonmetro” counties include some combination of open countryside, rural towns (<2500 people) and urban areas with <50,000 people. We propose a composite scale for degree of rurality, based on individual scores using five established definitions (for further details see Study Design, Section 4 below). Limited rural access to medical care across four dimensions—people, place, providers, and payment—is well-documented, and access to specialists is even more limited. The disproportionate impact of substance use in rural populations, particularly opiates, raises additional concerns regarding treatment

with other controlled drugs, such as zolpidem. On the other hand, the generally wide safety profile and straightforward prescribing guidelines for zolpidem make it potentially attractive for rural settings. Although more rural than urban Americans lack access to in-home broadband internet (39% vs. 4%), a similar proportion use the Internet (69% vs. 75%), and overall Internet use is increasing at the same rate, making Internet CBT-I feasible. Our study addresses specific needs and knowledge gaps in rural settings.

We can examine HTE with an adequately-powered comparative effectiveness study. Previous studies suggest that characteristics such as sex, marital status, education, and occupation are generally not related to CBT-I outcomes, but these studies have not been powered to detect such differences. Greater pre-treatment severity and older age are associated with larger changes in quantitative sleep characteristics, but smaller changes in categorical outcomes, whereas concurrent sleep medication does not appear to affect CBT-I outcomes. Short objective sleep duration and medical/psychiatric comorbidities are associated with smaller treatment effects. Most medication trials select insomnia patients on the basis of specific symptoms that match the medication's pharmacokinetics.

However, multiple sleep symptoms are the most common phenotype, and symptoms change over time. Thus, we do not know if specific insomnia symptoms affect HTE. Our study will address which treatment is most effective for which patient.

DECISIONAL DILEMMA: Patients, clinicians, and other stakeholders are concerned about the health consequences of inadequate sleep, but they face a quandary in choosing a treatment for CID. Whereas CBT-I is recommended by current guidelines and often preferred by patients, many providers do not know how to access it. BzRA are more familiar to patients and providers, but can have significant side effects. Existing evidence does not provide adequate guidance for choosing between these efficacious treatments. A long-term, real-world comparative effectiveness study will provide evidence about the relative benefits and harms of CBT-I, BzRAs, and combination treatment, and about who benefits most from which treatment—evidence that will help providers and patients make informed and individualized treatment choices.

SPECIFIC AIMS

To address current evidence gaps we aim to test the following specific aims:

Specific Aim 1A: To compare the effectiveness of medication preference (zolpidem or trazodone), Internet cognitive behavioral therapy for insomnia (CBT-I), and combination treatment (medication preference + CBT-I) for *insomnia symptoms over 12 months*. Hypothesis 1a: Internet CBT-I alone and combination treatment will be superior to medication preference alone in improving insomnia symptoms over 12 months. Hypothesis 1b: Individuals receiving combination treatment will use less medication at 12 months compared to individuals receiving medication alone.

1B: To compare the effects of treatment group assignment on insomnia symptoms, stratified by medication preference. Those randomized to the medication alone and combination treatment arms will be prescribed the preferred medication. These subgroups will be compared to those in the CBT-I alone arm whose provider indicated preference for that medication prior to randomization.

1C: Compare the effects of prescribed zolpidem versus trazodone on insomnia symptoms, within the medication and combination treatment arms of the study.

Specific Aim 2A: To compare the effectiveness of medication preference, Internet CBT-I, and combination treatment for key patient- centered outcomes (PCOs), including health-related quality of life, mood, cognition, fatigue, pain and other health outcomes (based on self-report) over 12 months. Hypothesis 2: CBT-I alone will be superior to both combination treatment and medication alone for improving PCOs over 12 months.

2B: To compare the effects of treatment group assignment on PCOs, stratified by medication preference. Those randomized to the medication alone and combination treatment arms will be prescribed the preferred medication. These subgroups will be compared to those in the CBT-I alone arm whose provider indicated preference for that medication prior to randomization.

2C: Compare the effects of prescribed zolpidem versus trazodone on PCOs, within the medication and combination treatment arms of the study.

Specific Aim 3A: To compare the adverse effects of medication preference, CBT-I, and combination treatment. Hypothesis 3: Adverse effects (e.g., falls) will be greater in the medication and combination treatment groups vs. CBT-I alone.

3B: To compare the effects of treatment group assignment on adverse events, stratified by medication preference. Those randomized to the medication alone and combination treatment arms will be prescribed the preferred medication. These subgroups will be compared to those in the CBT-I alone arm whose provider indicated preference for that medication prior to randomization.

3C: Compare the effects of prescribed zolpidem versus trazodone on adverse events, within the medication and combination treatment arms of the study.

Specific Aim 4: To conduct an exploratory analysis that will assess the potential for heterogeneity of treatment effects with medication preference, CBT-I, and combination treatment. We will assess whether treatment response varies by degree of rurality, as well as sociodemographic (age, sex, race, socio-economic status), health-related (insurance, comorbidities) and sleep-related factors (short sleep, insomnia treatment preferences).

COZI will address important knowledge gaps related to the treatment of a highly prevalent chronic condition with significant impact on PCOs. Our findings will lead to answers for patients, providers and other stakeholders addressing insomnia, improved health and function for millions of Americans, and sustainable changes in how insomnia is treated.

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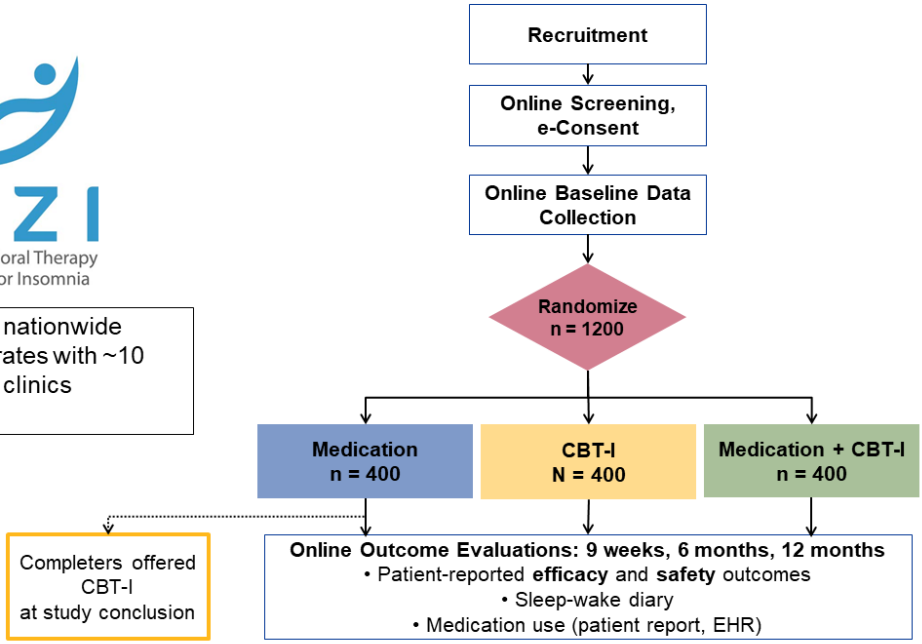
STUDY DESIGN

COZI is a 3-arm, randomized comparative effectiveness study. Masking is not possible given two very different treatment types. 1200 participants (400 per arm) will be randomized to 1) medication (zolpidem or trazodone); 2) SHUT); or 3) combination treatment (medication +CBT-I). Sleep and other PCOs, will be assessed via Internet questionnaires at post treatment (9 weeks), 6 and 12 months. Self-reported medication use and adverse events will be assessed at all scheduled follow-ups as well as at some additional time points (See assessment grid).

COZI

Cognitive Behavioral Therapy and Zolpidem for Insomnia

- 8 research "hubs" nationwide
- Each hub collaborates with ~10 rural primary care clinics ("spokes")



METHODOLOGY

Study Population and Recruitment

Recruitment will occur in primary care practices in 8 large healthcare systems, each of which has significant coverage of patients in rural locations. The sites represent a diverse sample based on geography, socioeconomic status and race/ ethnicity. Study eligibility criteria were designed to be inclusive, to maximize the generalizability of study findings, and to ensure patient safety (see inclusion/exclusion criteria).

The development of recruitment methods involves collaboration between the RRC, hub research sites, and practices, and will be responsive to ongoing experience. Recruitment efforts will be aided by educational programs for physicians and clinic staff prior to study start-up, and by the development of branded recruitment materials in clinics (e.g., cards, brochures, posters).To facilitate a productive working relationship between the sites and practices around recruitment, we will engage in regular communication with the use of newsletters, relevant insomnia literature, and CME programs.

We will enroll patients with CID according to International Classification of Sleep Disorders (ICSD-3) terminology, or Insomnia Disorder in Diagnostic and Statistical Manual (DSM-5) terminology. We will confirm "caseness" using the Insomnia Severity Index (ISI) and a CID diagnostic checklist, administered during online screening. An ISI threshold of >10 has the optimal sensitivity and specificity for identifying insomnia "cases" in the general population (86.1% sensitivity and 87.7% specificity and thus constitutes our inclusion criteria.

To protect the safety of potential patients in COZI, Primary Care Providers (PCPs) who have a potentially eligible patient with CID will review the medical history and medication list to determine whether there are any obvious contributors that require further treatment or would increase risk of participation. Such conditions include depression and anxiety, and other sleep disorders, particularly sleep apnea and restless legs syndrome (RLS). We will also use the STOP-BANG questionnaire to assess risk of obstructive sleep apnea during the baseline visit, and return results to PCPs and patients. Specifically, we will identify whether patients are in the "green (0-2 points)," "yellow (3-4 points)," or "red (5-8 points)" zones for STOP-BANG scores, and provide appropriate recommendations for evaluation and treatment to PCPs for each level. We will not exclude any potential participant solely on the basis of STOP-BANG scores. When neck circumference (the "N" in STOP-BANG) are unavailable for participants, we will use modified (STOP-BA[N]G)scores. We will exclude patients who are older than 80 years, in order to minimize incidents of adverse cognitive events and falls. PCPs may order appropriate tests, such as home or laboratory sleep apnea testing, and change or add treatments for comorbid conditions. When patients present with clinically significant symptoms of other comorbid conditions (e.g., depression, anxiety, sleep apnea) the research team will provide results to the PCP so that they may plan for appropriate follow-up.

The RRC will assist in the implantation of ongoing participant retention strategies (see Table 1.).

Table 1. Participant Retention Strategies

Strategy	Details
Minimize participant burden	The online platform centralizes all interactions with COZI into a single point of contact and includes mobile notifications and individualized task lists to facilitate participant reporting
Provide desired benefits	For patients who join the trial in hopes of receiving CBT-I but are randomized into the medication only arm, we will offer a year of free CBT-I starting after the 12-month data collection period

Build in self-learning	COZI will support provide feedback to participants and PCPs on selected research assessments (ones that do not threaten the validity of testing study aims). Participants will also be a key audience for dissemination of study findings.
Build pride in joining	Study participants often express pride in joining in an important national study that will potentially help others. Regular newsletters and study updates will be delivered through the RICE app.
Express appreciation	Participants feel bonded to a study if they sense appreciation and a relationship. We will nurture relationships with texts and email follow-up reminders; 'thank yous' for data surveys; and quarterly newsletters.

COZI will employ a variety of options for recruitment. This flexibility will allow clinics to use methods that fit best into their current workflow while minimizing burden for both clinic staff/physicians and patients. These methods include (but are not necessarily limited to):

- EHR searches to identify potential study patients, followed by an invitation letter from the patient's PCP
- Self-referral by the patient via their PCP (e.g., in response to posters or brochures)
- Identification of potentially eligible patients by the PCP at the time of visit
- Review of medical records for scheduled patients to identify potential participants

After identifying a potentially eligible patient, the PCP will provide the patient with instructions for contacting the local hub research team by telephone or e-mail. In some instances, PCPs may also refer assenting patients to COZI hub research staff verbally or electronically (telephone or secure email). If the referral includes an email address, hub research staff will send participants an introductory email directing them to the study website for additional information and online screening. Alternatively, study staff may contact participants by telephone to complete initial screening.

Finally, at hub sites with the capacity to do so, we will program alerts in the EHR, designed to trigger for patients who meet inclusion/exclusion criteria. Upon obtaining the patients' initial assent, physicians will refer eligible patients to the study by making the appropriate selection in the EHR. PCPs may also refer appropriate patients who do not trigger an alert (e.g., a patient with new-onset insomnia) by placing a consult, order, or message to COZI in the EHR. In either scenario, the patient's information will be electronically transmitted to the study team for further assessment.

Regardless of the referral route, potentially eligible patients will meet the inclusion/exclusion criteria listed below.

Screening Procedures

Initial screening in conducted to ensure that every participant meets the following Inclusion/Exclusion criteria:

Inclusion Criteria:

- Age 18-80
- Meets DSM-5/ICSD-3 criteria for chronic insomnia disorder
- Insomnia Severity Index score > 10
- Regular internet and computer access
- Non-metropolitan/rural residence (Rurality Score $\geq$ 3)

Exclusion Criteria:

- Use of prescription hypnotic medication >2 times in the past week. Patients currently taking OTC medications (e.g., diphenhydramine, doxylamine) and naturopathic sleep aids (melatonin, valerian, chamomile, etc.) are permitted, at the discretion of the prescribing physician.
- Current cognitive or cognitive behavioral treatment for insomnia.
- Psychotic disorder
- Bipolar disorder
- Current substance use disorder
- Severe pulmonary disease that raises concerns regarding respiratory depression with sedative-hypnotic agents, as judged by the COZI Investigators.
- Cognitive impairment or dementia
- History of spontaneous or hypnotic-induced complex sleep behavior
- Delayed sleep phase disorder (DSPD)
- Shift work that includes working the night shift (between the hours of 12:00 a.m. - 6:00 a.m.)
- History of fall resulting in a fracture or other injury, in the past 12 months. Currently pregnant, planning to become pregnant, or breastfeeding
- Other severe or uncontrolled mental or physical disorders that would make participation difficult or unsafe
- Current use of opiate medication

Inclusion/exclusion criteria will be communicated to PCPs and provided in research recruitment materials (cards, flyers, etc.). We will verify inclusion/exclusion criteria during the online or telephone screening visit. We will confirm the presence of CID using a diagnostic checklist, and insomnia severity using the Insomnia Severity Index (ISI) during screening. An ISI threshold of >10 has the optimal sensitivity and specificity for identifying insomnia "cases" in the general population. Exclusion criteria are also addressed in the online/phone screen: hypnotic use; psychotic disorder; bipolar disorder; current substance use disorder; COPD or other severe pulmonary disease; cognitive impairment; history of complex sleep behavior; history of fracture or injurious fall within past 12 months; and current pregnancy, planning to become pregnant or breastfeeding.

Rurality of practices and participants will be determined by the COZI Rurality Score. The COZI Rurality Score was created by reviewing the existing national definitions of rurality and integrating those that do not overlap into a combined score. The COZI Rurality score includes % rural population, rural urban commuting area (RUCA) and urban influence code (UIC) scores, Centers for Medicaid and Medicare Services (CMS), and frontier and remote area (FAR) scores. (CMS scores in turn reflect Census Bureau-defined non-urbanized areas and health professional shortage area (HPSA) or medically underserved area/population MUA/P eligibility.) Utilization of the COZI Rurality Score allows for characterization of rurality across a continuum. Scores range from 0 (not at all rural) to 40 (highly rural); a score $\geq$3 is required for clinic/ patient participation.

The initial screening involves self-report information regarding demographics and general health information. Participant assent for screening will be obtained, per a written screening script. Screening may be conducted either online or by telephone; prospective participants may select their preferred method. For increased security, the online screening will be done using the Research Infrastructure Containing E-interventions (RICE) system developed at the University of Virginia under the leadership of Lee Ritterband, PhD, Digital Therapeutics Core Director.

For screenings conducted by telephone, the screener will begin with a brief description of the research study, interventions, and assessment procedures. If the patient expresses interest and gives verbal assent, staff will ask screening questions to determine eligibility. Staff will enter patient responses directly into the data base via web interface. If the patient is eligible to proceed and expresses interest, the screener will schedule a time for the patient to review the study consent form with the study coordinator. In states where required by law (Pennsylvania), a physician or licensed nurse practitioner will participate in the informed consent process.

Online web-based screening includes the same sequence of events except that the participant reads the material and selects their answer(s) Participants will be informed following the online screen if they are not eligible to proceed in the study. Eligible participants will be instructed to contact study staff to schedule their consent call. Study staff will also monitor online screening completions and will reach out to eligible participants to ensure that all eligible participants have the opportunity to schedule the consent call. If eligibility is questionable (as determined by decision rules to responses) participants will be notified that a staff member will call them to discuss the next step. During this call, clarification will be sought to determine eligibility.

Voluntary Informed Consent

After screening, hub research staff will send eligible participants an email including a study summary, consent form, and the URL for the study website. The website will also include the study summary and consent form. Participants will be encouraged to review both documents prior to the consent visit. During the consent visit, which will take place via telephone call or videoconference, the patient will have the opportunity to ask questions and request clarifications. After a discussion of study procedures, risks, benefits, and responsibilities, interested participants will electronically sign the consent form. Upon signing the consent, the participant will receive a signed, pdf copy of their consent via e-mail.

After informed consent has been obtained, the EHR will be used to verify the absence of exclusionary factors (i.e. fall risk, etc.). For those participants whose EHR is not accessible, hub research staff will contact the PCP to clarify any outstanding questions related to safety, eligibility and participation.

Baseline

Participants who are eligible after the initial telephone/online screening and consent visit will complete a set of self-report assessments via web interface (see Table below). Except as otherwise indicated, the same assessments will be used at the 9-week, 6-month, and 12-month evaluations. These assessments will allow us to address each of the specific aims of the study. We estimate the total time for completion of self-report assessments is 20-90 minutes (allowing 2.5 – 8 questions completed per minute).

Randomization

Following completion of the baseline assessment, eligible patients will be randomized to one of three interventions: Medication, Medication + CBT-I , or CBT-I, in a 1:1:1 ratio. The randomization will be stratified by enrollment hub and medication preference. The DCC will oversee randomization procedures. In brief, the study statistician at the DCC will provide each enrollment hub with a REDCap randomization form that will allow the study coordinator to perform randomization by enrollment hub, and stratified by medication preference (using a protected listing of random treatment assignment.

These listings will be generated using a Stata program that generates randomly permuted blocks of size 3 and 6, stratified by enrollment hub and medication preference.

Intervention

Medication

Medication will be prescribed by the participant's primary care provider (PCP) or, in the event that the patient does not have a PCP, by a COZI study physician. Following randomization to either of the two medication arms (i.e., medication alone or medication + CBT-I), the participant and prescribing provider (PCP or COZI physician) will be notified by the study team. The patient's prescribing provider (PCP or COZI physician) will then prescribe zolpidem or trazodone and monitor treatment throughout the one-year follow-up period as per usual care in this pragmatic trial. There is no difference in risk depending on whether the PCP or COZI physician prescribes. Providers will use their discretion in prescribing, guided by their patient's progress and standard clinical guidelines. For zolpidem, this will include a starting dosage of 5 mg, with an increase to 10 mg, if needed and based on response, for patients $\leq$65 years old. Trazodone, when prescribed for insomnia, is usually administered in doses of 25 – 100 mg, which is below the therapeutic range for depression treatment. In the COZI study, we will recommend a starting dose of 25 mg, with dose adjustments to a maximum of 100 mg at the discretion of the provider based on patient response. A standard order set will be provided to physicians, as well as a brief set of written instructions, with tips for optimal use of the medication (e.g., when the medication should be taken, frequency, dosage, etc.). This information will also be covered in the CME program provided prior to the start of recruitment. Frequency of medication use will be tracked as an outcome over the one-year follow-up period, based on self-report ascertained at regularly scheduled follow-ups. Note that, in contrast to medications for other health conditions, intermittent use several times per week, rather than every night, is often recommended for hypnotics (including zolpidem) in order to reduce dependence and tolerance. Intermittent dosing is efficacious for zolpidem and conforms to actual patterns of medication use. The effectiveness of intermittent dosing for trazodone is not well documented. Therefore, traditional measures of "adherence," based on the assumption of daily medication use, are not necessarily appropriate for medication in COZI, and might better be termed "pattern of use."

COZI Study Assessments

Category	Instrument	Primary/ Secondary/ Descriptive, Aim #[1]	Survey Total Score (18 max)	# Items	Assessment Points			
					Screen	Base	1, 9 Mos	9 Wks, 6 Mos, 12 Mos
Demographics	Demographics Questionnaire	D	N/A	14		X		
Degree of Rurality	COZI Rurality Score	D	N/A	1	X			
Insomnia	Insomnia Severity Index (ISI)	P1	18	7	X	X		X
Insomnia	DSM-5/ICSD-3 Insomnia Diagnosis	S1	N/A	7	X			X
Insomnia	Insomnia treatments	D	N/A	3		X		X
Sleep	SASS-Y (retrospective diary analogue)	S1; D4	N/A	16		X		X
Sleep	Pittsburgh Sleep Quality Index (PSQI)	S1	13	18		X		X
Sleep	Epworth Sleepiness Scale (ESS)	S1	13	8		X		X
Sleep apnea	STOP BANG[2]	D	N/A	9		X		
Circadian rhythms	Munich Chronotype Questionnaire (MCTQ)[3]	S1, D	10	6[3]		X		X
Sleep Moderators-Mediators	Dysfunctional Beliefs and Attitudes about Sleep	S4	12	10[4]		X		X
Moderators-Mediators	Treatment Credibility/ Expectancy	S4	11	5		X		
Moderators-Mediators	Client Satisfaction Questionnaire	S4	N/A	8		X		X
Mental Health: Depression	PHQ-8	S2	11	8		X		X
Mental Health: Anxiety	GAD-7	S2	12	7		X		X
Cognitive Health: Cognitive function	PROMIS Cognitive Function 2.0 8a	S2	16	8		X		X
Health: Fatigue	PROMIS Fatigue SF	S2	8	6		X		X
Health: Pain	PROMIS Pain Intensity SF 3a	S2	7	3		X		X
Health: Pain	PROMIS Pain Intensity SF 6a	S2	7	6		X		X
Health: Nocturia	Nocturia questionnaire	S2	N/A	3		X		X
Health: General	Medications, tobacco, alcohol, caffeine[5]	D	14	10 (estimated)		X	X	X

Health: General	Medical History Checklist	D	14	25		X		
Health: COVID related	COVID questionnaire	D, S4	N/A	10		X		X?
Health: Quality of life	Medical Outcome Survey SF-12	S2	10	12		X		X
Health: Quality of life	PROMIS Global health	S2	10	10		X		X
Adverse effects	Insomnia Treatment Side Effects	S3	15	3			X	X
Adverse effects	Falls	S3	10	10		X	X	X
Process measures	Exit interview if withdrawn	D	15	1			X	X
Global severity	Patient Global Impressions Severity	S1	13	1		X		X
Global improvement	Patient Global Impressions Improvement	S1	13	1				X
Total questions per assessment				228	7	223	24	175
Completion time, minutes[6]					1-3	27-87	3-8	22-70
Primary Outcomes				106				
Secondary Outcomes				78				
Sample descriptives				44				
Primary + Descriptive				150		146		122
Completion time, minutes[6]						19-59		16-50

[1]P = Primary Outcome. S = Secondary Outcome. D = Sample descriptive and/or HTE factor. Numbers indicate Specific Aim #.
[2]May need to exclude N = Neck Circumference
[3]SASS-Y and MCTQ instruments contain mostly overlapping questions. 6 = number of questions unique to MCTQ
[4]DBAS has short forms with either 10 or 16 items
[5]No set number of items; counted as 5 items for TOTAL number of items
[6]Estimated time for completion based on 2.5 – 8 questions/minute

CBT-I (via SHUTi program) Intervention

SHUTi is a self-guided, automated, interactive, and tailored web-based program modeled on the primary components of CBT-I: sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relapse prevention. Intervention content is metered out over time through 6 "Cores." Users obtain access to a new Core based on a time and event-based schedule (e.g., 7 days after completion of previous Core). This schedule is consistent with recommendations from the American Academy of Sleep Medicine deeming 6–8 sessions an "adequate treatment exposure." SHUTi uses online sleep diaries to track progress and to tailor treatment (e.g., assign a "sleep restriction" window). Each Core acts as an online analog for the weekly sessions of traditional CBT-I, and follows the same structure: 1) Core objectives (what will be learned and why it is important), 2) Review of previous week's homework and sleep diary data, 3) New intervention material, 4) Assignment of homework (treatment strategies for the coming week), and 5) Summary of the Core's main points. Intervention content is enhanced through interactive features including personalized goal-setting, graphical feedback based on participant-specific symptoms, animations/ illustrations, quizzes to test user knowledge, patient vignettes, and video-based expert explanation. Automated emails encourage program adherence. After completing the post-assessment battery and sleep diaries, individuals will have continued access to the online program for 1 year. Data will be collected through the 6 cores/diaries only.

CBT-I + Medication

Participants in the combined CBT-I + medication arm will complete procedures for each of the respective arms as described above.

Adverse Events Reporting

Patients in the medication conditions will receive printed material describing pharmacotherapy treatment, including instructions to discontinue use if serious side effects or other concerns arise. Adverse events will be monitored in two ways:

- Spontaneous Reporting: Participants and PCPs will be encouraged to report any side effects or adverse events during the intervention. The randomization assignment e-mail will encourage participants to contact their physician and the study team if they experience any AEs during the course of their intervention. Patients and physicians will be instructed on how to spontaneously report adverse events on-line or by telephone, 24 hours per day, 7 days per week, for the duration of the study. Serious adverse events will be followed up by telephone contact from the site coordinator within 24 hours, including assessments with the instruments described in the following paragraph. The intervention section of the study website will also include instructions for reporting AEs.
    - If a participant spontaneously indicates suicidal ideation during any contact with the study team, we will initiate a Suicide Risk Management Protocol (SRMP). This protocol includes procedures adapted from those previously utilized in online treatment studies of depression, including the PCORI funded Optimum study. The SRMP begins with an interview of the participant by the site Project Coordinator, following an online structured interview format. The online interview automatically generates a risk rating. These ratings are tied to specific recommended actions, ranging from the provision of information to contacting emergency authorities for a safety check. Each study site will generate a list of local mental health resources for the counties serving each primary care practice, in the event that such resources are needed.

- Questionnaire-Based Reporting: Side effects will be monitored with the Insomnia Side Effects and Insomnia Side Effects/Falls questionnaires, administered at each assessment battery. Patients will complete adverse effect checklists at 1 month, 9-week, 6-month, and 12-month follow-up evaluations. The checklist is adapted for insomnia treatment from the Frequency/Intensity/Burden (FIBSER) instrument. Scores >3 on any item will be reported to patients' physicians, and will be followed up with a telephone evaluation by study staff, at which point the Adverse Events checklist will be completed by the site coordinator to determine severity and assessment of causality. Results of this evaluation will be reported to the patient's physician, the Study Advisory Committee (SAC) and Data Safety Monitoring Board.

FOLLOW-UP

Participants in each of the three intervention conditions will complete follow-up assessments at 9 weeks, 6, and 12 months following the start of the intervention. These assessments will be conducted by Internet-based questionnaires. Refer to the Table above for specific assessments.

In addition to these time points, participants will be asked about falls and other adverse events at 1 month, 9 weeks, 6 months, 9 months, and 12 months following the start of intervention. The falls and adverse event questionnaires are estimated to take about 1-3 minutes.

Participants will be contacted by secure e-mail via University of Virginia's "Secure" email setting in order to prompt them to complete their follow-up assessments.

If we are unable to reach the participant by secure e-mail, we will attempt to contact him/her by telephone and/or email to encourage them to complete them.

DATA MANAGEMENT AND STUDY COORDINATION

*Data Management and Study Coordination***.** The Data Coordinating Center (DCC) at the SFCC (CPMC) has provided data management and study coordination services to large-scale multi-center studies for decades. Their services typically include provision of a standard Research Data System for data collection, editing, querying and cleaning and a study web site to facilitate data management and administration. The DCC also distributes and maintains the numbered memo system to archive all study-wide communication. While the COZI trial will utilize RICE (hosted by the University of Virginia) as the data collection platform, the data managers and statisticians at the DCC will be responsible for final data cleaning and we will utilize DCC servers for long-term storage of all data files and access to network services and SAS statistical software. DCC data managers will access and download data directly from the RICE platform using a secure connection. The DCC will oversee the DSMB and will perform the interim and final statistical analyses to address the specific aims of the COZI study. Finally, the DCC will track and manage all study publications and ancillary studies and ensure adherence to established publications and ancillary study guidelines.

STATISTICAL ANALYSIS PLAN

1. Outcomes

Definition of Insomnia Severity Index outcomes. Insomnia Severity Index (ISI)*:* The ISI is a 7-item patient-reported outcome that is well-validated as an insomnia outcome measure. The ISI has acceptable internal consistency (Cronbach's α=.76-.78); excellent face and content validity; correlates with sleep diaries, polysomnography, and interviews; and has 86.1% sensitivity and 87.7% specificity for detecting insomnia cases in the community. The ISI takes <5 minutes to complete, making it useful for clinical settings, and has been validated in Spanish. Scores range from 0 to 28, with the following interpretations: 0-7 (no clinically significant insomnia), 8-14 (subthreshold insomnia), 15-21 (clinical insomnia, moderate severity), and 22-28 (clinical insomnia, severe). The **primary endpoint** will be change in ISI score from baseline to 12 months. Secondary outcomes will be treatment response, using the established definition of ≥ 6 point reduction in ISI score from baseline to follow-up, and remission of insomnia, defined as ISI <8 at follow-up.

Definition of other patient-centered outcomes. The COZI Assessments Table summarizes other key patient-centered outcomes (PCOs) to be used in secondary analyses (classified as "S2" under variable type/aim). We will assess the comparative effectiveness of therapy on PCOs that have not been extensively studied in prior insomnia studies. Our outcomes were informed by patient survey results.

Safety outcomes. Safety outcomes, including self-reported falls and other insomnia treatment side effects, are indicated in the COZI Assessments Table under the variable type/aim category "S3".

2. Data Analysis

Assessment of balance between treatment arms. To assess balance of the treatment and control samples, we will compare participant characteristics by treatment arm, overall and stratified by recruitment hub. These checks will use linear, logistic, and other generalized linear models as appropriate to the distribution of each of the baseline covariates. Baseline variables to be considered will include participant age, gender, race, body mass index, education, lifestyle factors, medical history, and degree of rurality.

Primary Analysis. Our causal model posits that the 3 treatments will have differential effects on insomnia severity, measured by ISI, and on other PCOs. Primary analyses will be conducted by treatment assignment, without regard to treatment adherence; sensitivity analyses with multiple imputation of missing outcomes are described below. The primary analysis will estimate between-group differences using linear mixed models (LMMs) for repeated ISI scores at 9-wks, 6-mos, and 12-mos, adjusting for baseline score, with normalizing transformation as needed. The primary analysis will model treatment differences as constant across outcome visits. Within-site and within-participant correlation will be accounted for using nested random effects. This approach makes efficient use of partial data for participants with incomplete follow-up data. LMMs will also be used for continuous secondary PCO outcomes, after normalization if needed Adverse events will be compared using generalized linear mixed models (GLMMs) or exact methods, depending on frequency; a negative binomial GLMM will be used for falls.

*Sensitivity Analyses***.** Extensive baseline data will be collected on baseline factors known to affect sleep quality, which will be reported by treatment assignment. In addition, sensitivity analyses will be conducted adjusting for any imbalanced baseline factors that can be shown to affect outcomes. Additional sensitivity analyses will check for variation in between-group differences across the three follow-up visits.

Heterogeneity of Treatment Effects. Powerful significant effect modifiers may help identify subgroups in which one treatment is clearly preferable or contraindicated. For example, although many patients with CID will have had exposure to hypnotics and other insomnia medications, we do anticipate that some will be naïve to medication treatment. We can ascertain prior medication treatment by self-report and EHR review. We expect nearly all patients will be naïve to structured behavioral treatment. We can address prior treatment experience in subgroup analyses as part of the broader heterogeneity of treatment effect analyses. To assess HTE, we will add interactions between treatment group and the hypothesized effect modifier to LMMs for the primary analysis. Within-subgroup treatment effects will only be reported if the test for effect modification is statistically significant at $P<0.05$; all pre-specified subgroup analyses will be reported. In exploratory analysis, we will use the Least Absolute Shrinkage and Selection Operator (LASSO) to develop a multivariate model predicting differential treatment response. Finally, we will assess between-site differences in treatment effects.

Treatment Effects among candidates for Zolpidem or Trazodone. The methods proposed for the primary analyses will also be implemented within the two subgroups of participants identified by their provider as candidates for zolpidem or trazodone before randomization. This preference will be a stratification factor in the randomization, thereby ensuring balance in medication preference across all treatment arms of the study. Using this strategy, zolpidem/trazodone users in the medication only and combined treatment groups can be compared to those in the CBT-I arm with the same medication preference, which avoids confounding of the primary between-group comparisons. Likewise, overall between-arm comparisons will be unconfounded by this factor for the same reasons. Nevertheless, we will include an indicator for trazodone/zolpidem preference in models that test overall between-group comparisons, to account for the stratification of the randomization.

Head-to-head comparisons of Zolpidem vs Trazodone. We will also compare the associations of zolpidem vs trazodone (in the medication alone and combined therapy arms) with study outcomes using LMMs and GLMMs as appropriate. For these head-to-head comparisons of zolpidem to trazodone, which will be confounded by indication, we will develop propensity scores using multivariate logistic models with provider preference for zolpidem as the outcome, and predictors including factors that we hypothesize influence medication preference, informed by the literature and our own provider surveys. These will include patient factors such as age and gender, health status (e.g. frailty) and comorbidities, history of substance abuse or concurrent opioid use, and depression. Other factors that drive medication preference may occur at the provider or practice level. Such factors, e.g., concern that zolpidem is a controlled substance, will be considered for inclusion as nested random effects in the propensity score model. We will be careful to accommodate non-linearities and between-factor interactions in developing the propensity score model. Because propensity score model development will be conducted without regard to ISI, inflation of type-I error by model selection is not a concern. In addition, we will consider inclusion of nested random effects for center and provider in the logistic propensity score model, which has been shown to reduce bias in some circumstances. Propensity scores will then be estimated by the fitted probability of the observed provider choice, based on the final model. After checking for the overlap of the propensity score distributions between the zolpidem and trazodone groups, we will incorporate the propensity scores in outcome models comparing ISI scores as inverse probability weights.

Missing Data. Although extensive efforts will be made to maximize retention and minimize missing data, some missing data is inevitable. We will record and report reasons for dropout and missing data. The proposed LMMs will provide consistent estimates as long as the data are covariate-dependent missing at random (CD-MAR), the model includes the covariates justifying CD-MAR, and both its fixed and

random components are correctly specified. Using sensitivity analyses, we will multiply impute missing outcomes, first under the standard CD- MAR assumption, and then under plausible missing-not-at-random scenarios—for example, under the hypothesis that ISI scores are systematically lower than expected under CD-MAR after dropout in the CBT-I arm. Multiply imputed data will be analyzed using standard methods that account for uncertainty due to missingness.

Multiple comparisons. For the primary outcome, ISI scores, hypothesis testing for between-arm treatment differences will be conducted using the Hochberg procedure, a more powerful alternative to Bonferroni correction, to achieve a familywise error rate (FWER) of 5%. The Hochberg procedure will also be used for the additional secondary outcomes. Because power in the HTE analyses will be relatively limited, as shown below, a false discovery rate (FDR) of 20% will be targeted. To preserve power, no corrections will be made for multiplicity in comparing adverse event rates.

3. Frequency of Analysis and Stopping Rules

A statistical analyst at the DCC will analyze the primary and secondary outcomes after all participants have completed the 12-month follow-up and the final dataset is cleaned and released for analysis. Interim reports including limited analyses will be prepared for presentation to the DSMB during bi-annual meetings over the course of data collection. Interim reports will be derived from the database as it exists on pre-specified dates, and full copies of the database at the time of each interim analysis will be archived. These reports will generally include progress in recruitment and participant status, descriptives and safety outcomes (overall, by recruitment hub, and by masked treatment assignment). All tables shown by masked treatment assignment will be shared with the DSMB during the closed session of each meeting.

We will not apply any stopping rules for effectiveness, but may implement stopping rules for safety if suggested by the DSMB.

4. Adherence.

Conceptually, adherence to behavioral and pharmacologic interventions is quite different: We aim for patients to follow behavioral recommendations every day, whereas optimal adherence to hypnotic medication (for efficacy and safety) may involve less-than-nightly use. Adherence to CBT-I will be measured using automatically collected records of access to the system (e.g., core completions, diaries). Adherence to medication will be assessed using retrospective self- report of frequency of use. In both cases, these data may not reflect true adherence. We will use GLMMs to identify independent baseline correlates of adherence within each arm. We will also assess the association of adherence with ISI and other PROs within each arm. Because no common, valid adherence measure is available for all 3 treatment arms, correlates of adherence may differ. We will therefore exercise caution in interpreting mediation of treatment assignment by adherence and will not estimate between-group differences in treatment efficacy by adherence.

5. Blinding

The patient and treating physician will be notified of the treatment assignment following randomization and completion of the baseline questionnaire. Blinding of patients, treating physicians and COZI project staff who will be interacting with patients or working with data is not possible given two very different treatment types. However, the COZI study principal investigators (Drs. Stone and Buysse) will be blinded to any study results until after all data collection is complete and a final dataset is ready for analysis.

6. Sample Size and Power (Minimum Detectable Effects [MDEs])

Assuming 25% attrition by 12 months, and within-subject correlations between follow-up ISI scores of 0.67 and between baseline and follow-up scores of 0.4 [L. Ritterband, personal communication], 400 patients per group will provide 80% power in 2-sided tests to detect standardized between-group differences of .20 standard deviations (SDs) in the primary outcome. These estimates are obtained using a conservative type-I error rate of 0.05/3, as would obtain under the Hochberg procedure if only one of the three pairwise null hypotheses can be rejected, and would shrink if > 1 can be rejected. Based on results of EHR queries of COZI practices, we expect approximately 25% of COZI patients will be referred by practitioners who indicated preference for zolpidem, whereas 75% may favor trazodone. These proportions would be expected yield 100 zolpidem users and 300 trazodone users in the medication alone and combined arms of the study, and similar numbers of patients in the CBT-I only arm whose provider indicated preference for zolpidem or trazodone, respectively. However, we have calculated power for a wider possible range of preference proportions (50, 75, and 90% trazodone preference; and corresponding proportions of 50, 25 and 10% zolpidem preference). MDE estimates for subgroup comparisons (Aims 1B and 1C) across this range of scenarios based on the primary outcome (change in ISI) are shown in Table 9.

Table 9. MDEs (SD units) for Subgroup Comparisons involving Trazodone vs Zolpidem			
Trazodone Preference, % (N per group)	50 (200)	75 (300)	90 (360)
Zolpidem Preference, % (N per group)	50 (200)	25 (100)	10 (40)
Aim 1B MDEs: Trazodone to CBT-I*	0.28	0.23	0.21
Aim 1B MDEs: Zolpidem to CBT-I*	0.28	0.40	0.63
Aim 1C MDEs: Trazodone to Zolpidem**	0.26	0.30	0.43

*Comparison to CBT-I group in the corresponding medication preference stratum

**Comparison of prescribed medications within the medication alone arm, or combined therapy arm, after penalization for the adjustment for propensity score

MDEs for overall between-group differences in other PCOs will be 0.16 SDs before penalization for multiple comparisons, and 0.20-0.21 SDs, using a conservative type-I error rate of .05/9 (Aim 2A). MDEs for Aim 2B will range from 0.21 to 0.63 SDs, depending on the proportions in the strata indicating preference for trazodone and zolpidem. For head-to-head comparisons of zolpidem to trazodone in the medication or combined therapy arms (Aim 2C), MDEs will be 0.26-0.43 SDs, again depending on stratum sizes. As noted above, epidemiologic evidence suggests that use of zolpidem and other hypnotics may have negative impacts on some PCOs such as cognition, as well as safety outcomes such as falls. In contrast, trazodone may have less harmful effects, or even beneficial effects for some outcomes such as cognition. Finally, for HTE analyses (Aim 4), MDEs for effect modification are shown in Table 10.

Table 10. Minimum Detectable Effect Modification (SDs)

ICC of Outcome	Proportion in Subgroup (%)		
	30	**40**	**50**
0.1	0.32	0.30	0.29
0.5	0.35	0.33	0.32
0.7	0.32	0.30	0.29
0.9	0.21	0.20	0.19

We will ensure that there is sufficient balance by medication preference (trazodone vs zolpidem) across all study arms through stratified randomization. In order to ensure that we will have at least 10% of study participants randomized in the zolpidem preference stratum, we will specify *a priori* time-points during the study timeline to assess and report distribution of medication preference to our DSMB; we will make adjustments to our recruitment plans as needed by extending enrollment or targeting practices that prefer a particular medication.

DISSEMINATION OF RESULTS AND PUBLICATION POLICY

Results will be posted on clinicaltrials.gov.

We will disseminate our findings to multiple stakeholder constituencies using methods tailored to each. We will work with our SAC and PSEC to develop strategies for dissemination to **patient constituencies**. Strategies will include publications in print and electronic media, web content, and podcasts. Dissemination to patients will also benefit from our partnerships with multiple **patient advocacy groups**, most notably Project Sleep and American Alliance for Healthy Sleep. We have previously partnered with these groups on a PCORI-funded engagement award and have published with them. The investigators have a strong history of dissemination to **scientific constituencies** via peer-reviewed publications, conference presentations, and invited talks. The investigators serve as Deputy, Associate, and Editorial Board members on all of the major sleep-focused journal, as outlined in investigator biosketches. Similar strategies can be used to disseminate information to **providers, health care systems, payors, and product manufacturers.** The investigators will publish and present not only in sleep specialty venues, but also in primary care and health care-focused journals and meetings. Publications and study reports will also include detailed information regarding study premise, design, implementation, measures, and findings. These details will permit reviewers, readers, and stakeholders to assess the study's internal and external validity (IR5). As leaders in the field of sleep medicine, the study investigators are in frequent contact with **professional sleep medicine organizations** such as the AASM, SRS, SRN, and SBSM, and serve in multiple volunteer roles. For example, Drs. Parthasarathy and Buysse presented a session on PCOR for the trainee program at the SLEEP 2018 meeting; Dr. Buysse and other investigators and consultants have served on numerous AASM consensus conference and guideline panels. Each of these organizations will disseminate study findings via existing communication tools. There is significant potential for the study findings to be **implemented in clinical practice** and improve delivery of care. We will de-brief patients and clinicians regarding their treatment experiences in COZI, and use their feedback to **develop a treatment manual for deploying zolpidem and/or CBT-I** in clinical practice. Our patient- stakeholder panel includes payors, purchasers, product manufacturers, and policymakers. Our professional sleep medicine organization partners advocate for legislation and regulations that promote patient access to high quality sleep care which end-users and decision-makers will use to make policy and treatment decisions.

We will adhere with all policies pertaining to PCORI-funded research in order to make the results available to study participants. We will make results available to study participants through multiple mechanisms: (A) Our co-investigator and stakeholder, Ms. Flygare of Project Sleep, will encourage enrollment of study participants in Project Sleep social media accounts in Twitter and Facebook. Upon study completion, we will post study results on these outlets and disseminate the study findings to the participants and wider membership of Project Sleep. (B) Study participants will have the opportunity to meet with study staff face-to-face for a debriefing at the end of their participation of their individual results that can be shared without compromising the integrity of the study. (C) We will populate a study website with peer-reviewed manuscripts from the study. Lay narratives and abstracts will also be posted on this website.

DURATION OF THE PROJECT

COZI will be 4-years in duration. This includes start-up preparations, 2 years of recruitment, follow-up assessments and study close-out.

COZI Study Abbreviations

BzRA	Benzodiazepine receptor agonists
CBSA	Core Based statistical area
CBT-I	Cognitive behavioral treatment of insomnia
CCC	Clinical Coordinating Center
CD-MAR	Covariate-dependent missing at random
CID	Chronic insomnia disorder
COZI	Comparative Effectiveness of Zolpidem and Cognitive Behavioral Therapy for Insomnia in Rural Adults
CMS	Centers for Medicaid and Medicare Services
CPMC	California Pacific Medical Center
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EC	Executive Committee
EHR	Electronic health record
FAR	Frontier and remote area
FDR	False discovery rate
FWER	Familywise error rate
GLMM	Generalized linear mixed model
HAC	Hub Advisory Committee
HPSA	Health professional shortage area
HTE	Heterogeneity of treatment effect
LMM	Linear mixed model
MSA	Metropolitan statistical area
MUA	Medically underserved area
MUAP	Medically underserved area and population
MUP	Medically underserved population
OMB	Office of Management and Budget
PCO	Patient centered outcome
PCP	Primary care practitioner (prescribing provider)
PCORI	Patient-Centered Outcomes Research Institute
PI	Principal Investigator
PSEC	Patient Stakeholder Engagement Core
RRC	Recruitment and Retention Center
RUCA	Rural urban commuting area
RUCC	Rural urban continuum code
SAC	Study Advisory Committee
SC	Steering Committee
SD	Standard deviation
SHUTi	Sleep Healthy Using the Internet
UCSF	University of California, San Francisco
UIC	Urban influence code
UPMC	University of Pittsburgh Medical Center