Dormir Mejor Study: Randomized Controlled Trial of a Culturally Adapted Digital Program of Cognitive-Behavioral Therapy for Insomnia for Spanish Speaking Latina/o Primary Care Patients

National Clinical Trial (NCT) Identified Number: NCT05353296

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Grant Title: Dormir Mejor Study: Randomized Controlled Trial of a Culturally Adapted Digital Program of Cognitive-Behavioral Therapy for Insomnia for Spanish Speaking Latina/o Primary Care Patients

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18 May 2022

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

All National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

18 May 2022

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

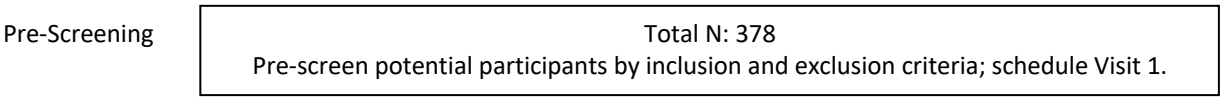
Title:	Dormir Mejor Study: Randomized Controlled Trial of a Culturally Adapted Digital Program of Cognitive-Behavioral Therapy for Insomnia for Spanish Speaking Latina/o Primary Care Patients
Grant Number:	HS024274
Study Description:	This a parallel-group, single-site, 2-arm Hybrid Type-1 effectiveness-implementation study . We will enroll 200 adults with positive chronic insomnia screen into a superiority randomized controlled trial to compare the effectiveness of a culturally-adapted Spanish-language digital program of CBT-I called Somryst (+ usual care, and sleep hygiene brochure) versus minimally enhanced usual care (mEUC) (usual care + sleep hygiene brochure). Follow-up assessments of insomnia symptoms and of secondary outcomes will be conducted at post-intervention (9 weeks) and 6 months follow-up by a staff member blinded to group assignment. Sleep duration and sleep efficiency will be assessed with actigraphy at baseline (prior to randomization) and at post-intervention (9 weeks). Patients will be randomly assigned in a 1:1 ratio to either the Culturally Adapted digital CBT-I program (Somryst) or minimally Enhanced Usual Care (mEUC) condition. Randomization will be generated by a computerized random-number sequence and held by the study statistician. The sequence will be unknown to research assistants enrolling patients. Our primary hypothesis is that patients randomized to the Somryst treatment condition will experience a greater improvement (from baseline) in the Insomnia Severity Index (ISI) at post-intervention (9 weeks) compared to those randomized to mEUC, and scores will continue to be better than mEUC patients at 6 months post-intervention. The null hypothesis is that there will be no difference in the ISI scores between patients randomized to the Somryst treatment versus those assigned to mEUC.
Objectives:	The primary objective of the proposed study is to examine the effectiveness of a culturally adapted digital CBT-I program compared to minimally enhanced usual care (mEUC) on primary outcomes: reduction in insomnia symptoms at 9 weeks, and 6 months post-intervention using a standard scale. Secondary outcomes will include quality of life, daytime sleepiness, satisfaction with care, sleep quality, and self-reported and actigraphy-assessed wake after sleep onset as well as self-reported sleep onset latency at post-intervention. Exploratory outcomes will include actigraphy-assessed sleep duration and sleep efficiency.

Endpoints:	Primary Endpoint: Insomnia symptoms will be assessed at baseline, at 9 weeks (post-intervention) and at 6 months post-intervention follow-up using the ISI. Secondary Endpoints: Health-related quality of life will be assessed through the validated Short-Form 12 (SF-12), Day time sleepiness will be measured with the 8-item Epworth Sleepiness Scale at baseline, at 9-weeks, and 6-months; Satisfaction with care will be measured using a question adapted for this trial asking patients to rate the quality of professional care they have received for their symptoms of insomnia at post-intervention and 6 -months; Wake after sleep onset will be measured with self-report and actigraphy, and sleep onset latency will be measured with self-report at post-intervention. Sleep quality will be measured with the PSQI at baseline, 9 weeks, and 6-months. Sleep duration and sleep efficiency will be measured continuously and unobtrusively for 14 days at baseline and for 14-days post-intervention using the ActiWatch SpectrumPRO, an actigraphy-based device.
Study Population:	Two hundred Latina/o adult patients from primary care clinics affiliated with Columbia University Irving Medical Center and New York Presbyterian Hospital (the Ambulatory Care Network) that serves underserved communities across New York City will be enrolled into the study. Patients will be Spanish speaking or bilingual (English and Spanish) adults with moderate to severe insomnia symptoms as documented on initial eligibility screen, who are interested in receiving digital care to improve their insomnia in Spanish.
Phase or Stage: Description of Sites/Facilities Enrolling Participants:	*Phase III trial* Patients will be recruited through flyers, email, telephone, and primary care provider referrals from primary care clinics affiliated with Ambulatory Care Network (ACN) of New York Presbyterian Hospital (NYPH). The catchment areas are the ACN clinics of NYPH, which serve 1.4 million individuals in NYC, including low socioeconomic and racially/ethnically diverse communities in NYC such as Washington Heights, Inwood, Harlem, and the Southwest Bronx, as well as geographically broader communities, including Queens. This is a single-site study and the site is not outside of the United States.

Description of Study Intervention/Experimental Manipulation:	Study candidates who meet initial eligibility criteria and consent to participate will be invited for an online virtual or in-person visit dependent on participant preference where they will complete a baseline sociodemographic and psychosocial survey battery, and be asked to complete a daily sleep diary for 14 days and to wear an actigraph (Actiwatch) that will be mailed to them to capture continuous objective sleep data on sleep duration and sleep efficiency for 14 days. Participants will be asked to return their actiwatch via mail. After completing the baseline assessment, patients will be randomly assigned in a 1:1 ratio to either the intervention condition (Somryst) or the comparator condition (Minimally Enhanced Usual Care (mEUC). Patients in the intervention group will receive the culturally adapted digital CBT-I (Somryst), usual care by their PCP and a sleep hygiene brochure. Patients will also be trained on how to record their daily sleep diaries using a smartphone diary; and will receive prompts on their smartphones or emails to remind them when to complete the daily sleep diaries. Patients randomized to the control group will receive minimally enhanced usual care (mEUC), which will include the usual care provided by their PCP, and an informational brochure on sleep hygiene. Patients in both groups will have their insomnia severity assessed again at 9-weeks post-intervention and at 6-months follow-up. Patients in both groups will also wear the Actiwatch Spectrum Pro to objectively assess sleep for 2 weeks after enrollment and again at the post-intervention assessment.
Study Duration:	8 months
Participant Duration:	8 months

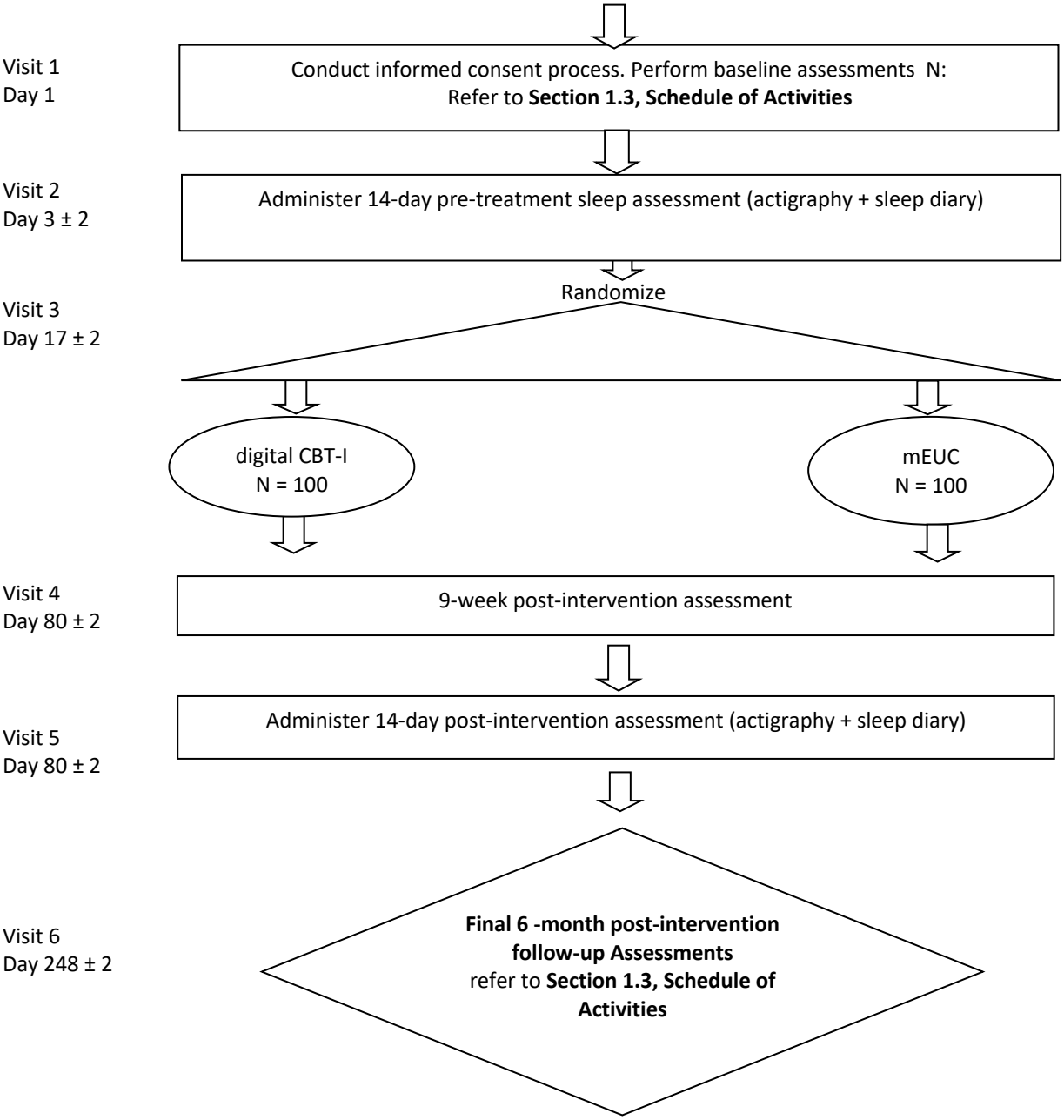
1.2 SCHEMA

Figure 1. Flow Diagram of RCT Study Design



Day -30 to Day 1

18 May 2022



1.3 SCHEDULE OF ACTIVITIES

After the cultural adaptation of Somryst developed in study 1, we will then enroll 200 patients into the RCT to compare the effectiveness of the culturally adapted digital program of CBT-I (Spanish Somryst) to minimally enhanced usual care and to determine cost-effectiveness of the intervention. Summary data from our pilot study indicate that 94 people were screened over 6 months, 52% were found eligible, and 71% completed the study. In particular, our screening in one primary care clinic over two months resulted in 22 people screened, 77% were eligible, and 71% completed the first focus group. Our pilot data indicate that we are able to screen 8 patients/month and enroll patients/month from one clinic and that an accrual rate of 12/month from multiple clinics is reasonable. The specific list of measures and schedules of activities are represented in Table 1.

Table 1. List of Measures and Schedule of Activities

	Screening/ Enrollment	**Baseline**	**Pre-Tx**	**Treatment**	**Post-Tx (9 weeks)**	**6-mo Follow -Up**
Procedure/Assessment/Follow -Up Windows	Virtual or in person	Virtual or in person	14 days before tx	Through Week 9 of Study	Post-Tx (9 weeks)	6-mo Post-Tx
Sociodemographic information	X					
Insomnia Severity Index	X	X		X	X	X
Informed Consent/Enrollment	X					
Permission for Future Contact and Use	X					
Sleep and Depression Medicines	X				X	X
Sleep Disorder	X					
CAGE Assessment	X					
Assessment for Bipolar/Psychosis/ Schizophrenia	X					
Health Care Coverage	X					
Assessment for Cognitive Impairment	X					
Language Proficiency	X					
Technology Use	X					
Referral/Contact Information	X					
Randomization				X		
Generalized Anxiety Disorder (GAD-7)		X		X	X	X
Epworth Sleepiness Scale (ESS)	X	X			X	X

Pittsburgh Sleep Quality Index (PSQI)		X			X	X
Quality of Life (SF-12)		X			X	X
Satisfaction with Care (PACIC)		X			X	X
Health Literacy		X				
Penn State Worry Questionnaire (PSWQ)		X				
Personal Health Questionnaire Depression Scale (PHQ-8)		X		X		
Health Care Utilization		X			X	X
Medical History		X				
Dysfunctional Attitudes and Beliefs about Sleep (DBAS-16)		X			X	X
Hospitalization					X	X
Acceptability and satisfaction with intervention					X	
Actigraphy			X		X	
Usability and Net promoter questionnaire					X[a]	
Sleep Diary			X		X	
Adverse Events				X	X	X

Notes: [a]Usability and Net promoter questionnaire will be asked once at the beginning of the post-tx actigraphy assessment period and will only be included for those who were randomized for Somryst treatment

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic insomnia—dissatisfaction with sleep quantity or sleep quality that is associated with difficulty initiating or maintaining sleep, or waking too early, and with impaired daytime functioning for at least three months— is a national public health problem.[1,2] It is the most prevalent sleep disorder in the US and is associated with poor health, increased risk of death, and significant economic costs.[3–5] Over 30 million US adults and nearly 20% of primary care patients suffer from chronic insomnia.[6–9] Importantly, the prevalence of insomnia is significantly higher in Hispanics (26.5%) than non-Hispanic Whites (22.5%),10 and this disparity is widening over time.[10]

National polls suggest that 20% of adults seek treatment from a health care provider to manage their insomnia, and primary care providers commonly serve as the first source of treatment.[11,12] Cognitive behavioral therapy for insomnia is a robustly effective psychological intervention for treatment of insomnia with sustained benefits,[13,14] and is recommended over medications as the first-line treatment for chronic insomnia.[15–17] Unfortunately, few receive this standard of care. Further, pharmacotherapy far exceeds use of CBT-I despite provider concerns about adverse effects from medications and patient preference for behavioral treatments.[17–20] Hispanics, and particularly those with limited English Proficiency, are even less likely than non-Hispanic Whites to have access to high quality evidence-based behavioral health care such as CBT-I, [21–23] primarily because of the lack of available qualified bilingual behavioral providers trained to deliver CBT-I in Spanish and costs.[24] Given the increasing prevalence of insomnia among Hispanics, and the linguistic realities of today's behavioral healthcare work force, the demand for bilingual behavioral health providers equipped to deliver CBT-I in Spanish significantly outweighs the supply. Advances in health information technology such as self-guided digital treatments represent an innovative and scalable means to address the supply and demand imbalance that perpetuates mental health care disparities; however, its implementation in underserved communities remains elusive.

Recent technological advances in ehealth or digital health demonstrate great promise for improving access to CBT-I: self-guided CBT-I delivered via an online web-based platform is as effective as CBT-I delivered in-person.[25–32] However, the randomized controlled trials (RCTs) that tested the effectiveness of digital versions of CBT-I were conducted outside of the primary care context in English-fluent, high socioeconomic status (SES), high health literacy, and non-Hispanic White samples.[33–35] As such, extant digital programs of CBT-I have not been adapted for use among these underserved patient populations. Further, data on the barriers and facilitators of implementation of these digital behavioral treatments in underserved racial/ethnic minority populations were rarely collected or used to support its integration into primary care.

This proposed study will use a Hybrid trial type 1 effectiveness-implementation study design that leverages recent technological advances in digital health to enroll 200 Spanish-speaking Hispanic primary care patients with chronic insomnia into an RCT that compares the effectiveness of a culturally adapted

digital program of CBT-I with enhanced usual care for insomnia. We will also concurrently assess the implementation context using a mixed methods approach.

2.2 BACKGROUND

Chronic insomnia is a national public health problem. It is the most prevalent sleep disorder in the United States (US), and is defined as dissatisfaction with sleep quantity or sleep quality that is associated with difficulty initiating or maintaining sleep, or waking too early, and is accompanied by impaired daytime functioning for at least three months.[1,2] Over 30 million Americans (10%),[3,4] and nearly 20% of primary care patients[6,7,36,37] suffer from chronic insomnia, which persists for at least 3 years in 50-85% of those with the condition.[37–39] Chronic insomnia also exerts a significant toll on the US economy. Over $14 billion dollars are spent annually on direct costs associated with insomnia-attributable health care services or sleep aids,[3,18] and insomnia is associated with higher rates of health care utilization (both medical and psychiatric care), daytime impairment, and occupational impairment.[3,7,18] Indirect costs associated with insomnia are as high as $28 to $57 billion, when considering lost workplace productivity due to absenteeism and presenteeism (attending work even while sick, fatigued), accidents, and reduced quality of life.[3,40–42]

Chronic insomnia is associated with poor health and increased risk of death. Insomnia is linked to increased risk of incident hypertension, metabolic syndrome, myocardial infarction, stroke,[3,18,43–48] and cardiovascular and all-cause mortality.[43,49] Insomnia also has a bidirectional association with psychiatric disorders. In many cases, insomnia co-occurs with, results from, or precedes the onset of depression and anxiety.[50–54] For example, over 33% of people with insomnia also have a mental disorder.[4]

Latina/os bear greater risk of chronic insomnia and sociocultural stressors may be important determinants of insomnia for Hispanic adults. Importantly, the prevalence of insomnia is significantly higher among Hispanics (26.5%) than non-Hispanic Whites (22.5%),[55] and this disparity is widening over time.[10] Temporal analyses using the National Health Interview Survey indicate that the age-adjusted prevalence of insomnia among Hispanic/Latino adults was 16.6% in 2002 compared to 19.3% in 2012.[10] Additionally, analyses of over 5,000 participants in the Hispanic Community Health Study/Study of Latinos indicates that acculturative stress, or the stress associated with integration and adaptation to the US mainland, is strongly predictive of insomnia severity (Exp(b)=1.15 (95% CI: 1.11, 1.18).[56] As such, resolution of acculturative stress may be an important intervention target in behavioral treatments for insomnia targeting Hispanics.

Chronic insomnia is undertreated in the usual primary care setting. National polls suggest that 60% of adults take some action to manage their insomnia while the remaining 40% do nothing at all or assume it will go away with time.[11,12] Only 20% of adults seek treatment from a health care provider for their insomnia, and primary care providers serve as the first source of treatment.[11,12,40] However, primary care providers often consider insomnia to be secondary to other psychological or physical health issues, and behavioral treatments for insomnia are rarely considered or available.[57,58] Indeed, a recent review identified a number of primary care provider barriers to insomnia treatment including: inadequate training, time-constrained office visits, lack of discussion of sleep issues, inaccurate beliefs by both patients and providers about the importance of sleep problems, the perception among providers that

insomnia treatments are ineffective and associated with significant risks, and the lack of a research base showing that treatment of insomnia improves outcomes and co-morbid conditions.[18] These barriers contribute to an overall underdiagnosis and undertreatment of chronic insomnia in the primary care setting.[18]

Cognitive behavioral therapy for insomnia (CBT-I), a robustly effective psychological treatment with large effect sizes and proven long-term benefit over medications, is the recommended first-line of treatment for insomnia. Pharmacotherapy (benzodiazepine receptor agonists and non-benzodiazepines [sedating antidepressants]) and CBT-I are two treatments with considerable evidence to support their effectiveness in the clinical management of insomnia.[38] Numerous RCTs and meta-analyses have shown that, for the average patient included in these trials, pharmacotherapy and CBT-I are effective, at least in the short term.[33,37,59–62] Pharmacotherapy offers more immediate symptom relief over the first 10 days, but does not, on average, maintain these improvements after medication is discontinued.[38] In contrast, CBT-I, which combines cognitive therapy to address maladaptive beliefs and expectations about sleep, with behavioral treatments (e.g., sleep restriction, stimulus control), often implemented over 6-8 weeks, results in more sustained benefits over time; CBT-I also has large effect sizes (e.g., wake after sleep onset improved by 26 minutes (95%CI: 15.48, 36.52).[13,14,38,63] Thus, clinical guidelines and systematic reviews encourage a trial of CBT-I first before pharmacotherapy is initiated.[38,64]

Use of pharmacotherapy far exceeds use of CBT-I for the treatment of chronic insomnia in the primary care setting despite growing evidence for major adverse drug effects from sleep medications.[16] Use of the commonly prescribed hypnotic, zolpidem tartrate (Ambien), was implicated in 11.5% of adult psychiatric medication adverse drug emergency department (ED) visits in 2009-2011, a rate which was markedly higher than that of any other drug.[65] Zolpidem was also implicated in 32.1% of all psychiatric medication ED visits for falls or head injuries.[65] Concerns about sleep medication side effects – dependence, and adverse drug events – loom large among both patients and primary care providers.[18] Importantly, when offered a choice, up to 75% of patients prefer behavioral treatments over pharmacotherapy for the treatment of psychiatric disorders such as insomnia.[17] Thus, there is an urgent need to expand access to evidence based and patient-preferred alternatives to pharmacotherapy for insomnia in the primary care setting.

Latina/os are less likely to have access to high quality behavioral health care, such as CBT-I, and this is especially true for Spanish-speakers. On average, Hispanics receive lower quality mental health care than their non-Hispanic White counterparts.[21–23] Limited English proficiency patients experience greater barriers to receipt of comprehensive behavioral health care. Indeed, 20% of Spanish speakers do not seek healthcare because of language barriers.[22] Given the rise of insomnia among Hispanics, and the linguistic realities of today's behavioral healthcare work force, the demand for bilingual behavioral health providers equipped to deliver CBT-I in Spanish significantly outweighs the supply.

While cognitive-behavioral therapy for insomnia is a robustly effective treatment with structured core components that can be adapted and tailored for use among underserved populations, no extant studies of CBT-I have targeted Spanish speakers. We conducted a systematic review of behavioral treatments for sleep problems to determine whether these treatments were adapted for vulnerable populations. Of the 22 studies included, 8 focused on insomnia and only 5 contained some form of adaptation. Modifications included accommodating the setting and length of the intervention. No modifications were made for Spanish language or other sociocultural factors. Yet, racial/ethnic and language minorities who receive a

culturally adapted intervention versus an unadapted intervention exhibit superior treatment and retention outcomes.[66,67]

Limited access and high cost are key barriers to the wide implementation of in-person CBT-I in primary care. A lack of awareness, limited availability of qualified behavioral providers, and the high cost of CBT-I have impeded its uptake in primary care.[18] Indeed, "could not afford cost" is often cited as the most common reason among adults aged 18 and older for not receiving mental health services.[68] Primary care providers are also not well informed about how to refer their patients for behavioral interventions. Thus, there is a pressing need for low-cost, scalable behavioral interventions for chronic insomnia.

The RCTs testing CBT-I excluded Spanish-speakers. Many of the RCTs testing CBT-I had stringent inclusion criteria and were conducted in academic research centers, among patients with high socioeconomic status (mean education is 16.4 years) and with high levels of health literacy and numeracy.[33,34,69,70] The RCTs that were conducted in community settings [71–73] often did not include active comparators, were underpowered,[71] or did not include Spanish speakers.[35,74]

Although recent technological advances in e-health show great promise for improving access to CBT-I, most of these interventions have not been implemented in underserved racial/ethnic communities such as Hispanic communities. Internet-based CBT-I produces reductions in insomnia that are comparable to those achieved through in-person CBT-I.[25,29–32] However, none of the extant digital CBT-I platforms are available in Spanish. Behavioral interventions that leverage recent advances in e-health may be able to capitalize on the increasing rates of Internet use among Hispanic US adults to close this behavioral healthcare access gap, and address mental health care disparities. Indeed, Internet penetration among Hispanics in the US is at an all-time high, with 51% of Spanish-speaking and English-speaking Hispanic adults aged 18 and older reporting accessing the Internet via broadband at home, compared to 66% of non-Hispanic Whites.[75] Hispanics also have mobile devices such as smartphones and tablet computers in shares similar to Whites[76] and Hispanics are more likely than Whites to use their smartphones to access health information.[76] Advances in health information technology such as self-guided digital treatments represent an innovative and scalable means to address the supply and demand imbalance that perpetuates mental health care disparities; however its implementation in underserved communities remains elusive.

The specific barriers and facilitators for the successful implementation of digital CBT-I for Spanish speakers in primary care are unknown. While recent efforts within the Veterans Health Administration have focused on the implementation of in-person CBT-I,[24] no studies to date have conducted an assessment of the implementation context for digital treatments for insomnia. Further, data on the barriers and facilitators of implementation of these digital behavioral treatments in underserved racial/ethnic minority populations were rarely collected or used to support its integration into primary care. Emergent hybrid effectiveness-implementation study designs[77] offer great promise for the formal conduct of comparative effectiveness research and the identification of organizational, provider, and patient implementation factors that may affect successful integration of digital CBT-I. For example, this study design will allow us to assess treatment acceptability, providers' engagement with intervention implementation, patients' intervention self-efficacy, and compatibility of intervention with healthcare setting priorities.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

This study poses low risk of physical harm to participants. There may be immediate risks stemming from minimal discomfort from answering surveys about topics that are sensitive and personal in nature, and from wearing the Actiwatch that tracks sleep, but these are generally mild and go away quickly. Additionally, participants may experience initial tiredness/fatigue from the sleep restriction component of the intervention. Lastly, in taking part in the study there is the possibility of a loss of confidentiality or privacy.

2.3.2 KNOWN POTENTIAL BENEFITS

Immediate and long-term potential benefits include that participants randomized to the treatment arm will receive an interactive digital intervention designed to primarily improve insomnia and secondarily, health-related quality of life. Participants randomized to the minimally enhanced usual care control group will initially receive more information about the diagnosis and symptoms of insomnia in addition to information on sleep hygiene.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We are balancing the risk of discomfort in answering personal questions and from wearing the Actiwatch, the risk of increased sleepiness during sleep restriction for the intervention participants and risk of breach of privacy and confidentiality against testing a culturally adapted digital treatment for insomnia that could expand access to the gold standard of care for insomnia to Spanish-speaking adults at a reduced cost.

The risks to participants in this study are low. All participants will be informed that their responses are confidential, that they may end their participation at any time without explanation, and that ending their participation will in no way affect their future interactions with their health care providers or the study. To protect against risk, we will first obtain permission to participate from patients' PCPs before conducting study activities. We will emphasize to participants that they can discontinue the study interventions at any point during the trial.

The risk of loss of confidentiality will be minimized by securely storing data and minimizing the use of PHI. To ensure confidentiality, all data containing personal identifiers, used to track contact with patients, will be kept in a secure, password-protected, encrypted tracking program developed by the Data Management Unit (DMU) in the Department of Biostatistics in Columbia University's Mailman School of Public Health. DMU data systems have been certified by Columbia University Medical Center IT as secure for the storage of both research and patient care data. As part of this certification, the systems are audited regularly for security and regulatory compliance. Certification is based on HiTrust standards (https://hitrustalliance.net/benefits-hitrust-certification/). No paper documents with personal identifiers will be kept. Data collected via the smartphone app will be transmitted to a secured server that meets all HIPAA and other regulatory body requirements. Files downloaded from the web program will be stored on an encrypted study laptop and be password-protected. Study staff are assigned a user ID and password to assess the web program. Only the PI and research personnel listed on the study protocol will have access to the file password. No hardcopy data will be stored. The PI will be responsible for ensuring that

the confidentiality of the data is maintained at all times. All data will be obtained specifically and exclusively for research purposes.

The knowledge gained will help determine whether the culturally adapted digital intervention is effective at reducing insomnia symptoms compared to usual care. If effective, the dissemination of this intervention will greatly increase access to the first-line, evidence-based insomnia treatment in a primary care setting serving underserved patients, will reduce the burden of disease from chronic insomnia, and will reduce unnecessary adverse consequences of sleep medications for one of the fastest growing segments of the US population.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
The primary objective of the proposed study is to examine the effectiveness of a culturally adapted digital CBT-I program compared to minimally enhanced usual care (mEUC) on reduction in insomnia symptoms at post-intervention (9 weeks), and 6 months post intervention using a standard scale.	Change in insomnia symptoms (measured with the Insomnia Severity index) from baseline to post-intervention (9 weeks) and at 6 months post-intervention will serve as the primary endpoints.	Insomnia symptoms is the primary endpoint given that the intervention targets amelioration of insomnia symptoms.	
Secondary			
Health-related quality of life	Change in mean health-related quality of life score from baseline to post-intervention (9 weeks) will serve as a secondary endpoint. Health related quality of life will be assessed through the validated Short-Form 12 (SF-12), which is a 12-item self-report	Quality of life is included as a secondary endpoint because in Aim 2 Economic analyses will compare differences in mean health-related quality of life utilities (derived from SF-12 scores).	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	inventory that generically measures quality of life; it yields a measure of global health-related wellbeing as 8 domain-specific subscores.[82]		
Daytime sleepiness	Change in mean daytime sleepiness from baseline to post-intervention (9 weeks) follow-up will serve as a secondary endpoint. Sleepiness will be measured with the 8-item Epworth Sleepiness Scale, a brief, validated self-report scale of daytime sleepiness with excellent psychometric properties.[83]		
Satisfaction with care	Change in mean satisfaction with care from baseline to post-intervention (9 weeks) will serve as a secondary endpoint. Satisfaction with care will be measured using a question adapted for this trial asking patients to rate the quality of professional care they have received for their symptoms of insomnia.[85]		
Self-reported and actigraphy assessed wake after sleep onset.	Change in mean wake after sleep onset from baseline		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	post-intervention (9 weeks) will be a secondary endpoint. Self-reported wake after sleep onset will be recorded in a 14-day sleep diary and refers to the self-reported total number of minutes participants spent awake after they fell asleep. Actigraphy assessed wake after sleep onset will be measured with 14-days of wrist-actigraphy and refers to the total number of minutes participants spent awake after they fell asleep. Range: 24 hours Minimum value = 0 minutes (better) Maximum value = 1440 minutes (worse)		
Self-reported sleep onset latency	Change in sleep onset latency from baseline to post intervention (9 weeks). Sleep onset latency will be recorded in a 14-day sleep diary and refers to the number of minutes that it takes participants to fall asleep. Range: 24 hours Minimum value = 0 minutes (better) Maximum value = 1440 minutes (worse)		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Sleep quality	Change in sleep quality from baseline to post-intervention (9 weeks) will serve as a secondary endopoint. Sleep quality will be measured with the Pittsburgh Sleep Quality Index (PSQI), which has strong psychometric properties and is validated in Spanish.		
Tertiary/Exploratory			
Actigraphy assessed sleep duration and sleep efficiency	Change in actigraphy assessed sleep duration and sleep efficiency from baseline to post-intervention (9 weeks). Sleep duration and sleep efficiency will be measured continuously and unobtrusively for 14 days at baseline and post-intervention (9-weeks) assessment using the ActiWatch SpectrumPRO, a waterproof, lightweight, actigraphy-based device that measures physical activity continuously and can be worn for 24 hours daily. The validity of actigraphy for determining sleep duration in particular, compared with the gold		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	standard polysomnography, is excellent.[59]		

4 STUDY DESIGN

4.1 OVERALL DESIGN

We will use a Hybrid trial Type 1 effectiveness implementation study design[77] and a mixed methods approach to compare the effectiveness of culturally adapted-Somryst (+ usual care and a sleep hygiene brochure) vs. minimally enhanced usual care (mEUC; usual care plus sleep hygiene brochure). This is a parallel-group, single-site, 2-arm study.

Patients will be recruited through flyers, email, telephone, and primary care provider referrals from primary care clinics affiliated with Ambulatory Care Network (ACN) of New York Presbyterian Hospital (NYPH). The catchment areas are the ACN clinics of NYPH, which serve 1.4 million individuals in NYC, including low socioeconomic and racially/ethnically diverse communities in NYC such as Washington Heights, Inwood, Harlem, and the Southwest Bronx (31% African American; 61% Hispanic descent), as well as geographically broader communities, including Queens (11% African American; 25% Hispanic; 11% Asian/Pacific Islander).

We will enroll 200 adults who screen positive for chronic insomnia into an RCT that will compare the effectiveness the culturally-adapted digital CBT-I (Somryst) program versus minimally enhanced usual care (mEUC). Participants in the intervention arm will receive digital CBT-I, usual care by their PCP and a sleep hygiene brochure. Patients in the intervention group will also be trained on how to record their daily sleep diaries using a smartphone and will receive prompts on their smartphones or emails to remind them when to complete the daily sleep diaries. Patients randomized to the comparator group will receive minimally enhanced usual care, which will include usual care by their PCP and a sleep hygiene brochure. Patients in both groups will have their insomnia severity assessed again at post-intervention (9 weeks) and 6 months post-treatment. Patients in both groups will also wear the Actiwatch to objectively assess sleep for 2 weeks before randomization and again for the 2 weeks preceding the post-intervention assessment.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a single-site, parallel-group, 2-arm superiority randomized controlled trial of digital CBT-I (Somryst + usual care + sleep hygiene brochure) vs. minimally enhanced usual care (mEUC). Patients randomized

to the minimally EUC condition will continue to receive the typical standard of care in that clinic from their primary care provider (which may include pharmacotherapy). We have labeled the condition "minimally enhanced" because participants will be provided with a sleep hygiene brochure. Minimally EUC was chosen as the comparator because it is of high clinical relevance, will allow us to determine if the adapted digital CBT-I is superior to usual care, and addresses ethical issues (i.e., identifying but not treating insomnia).[78]

4.3 JUSTIFICATION FOR INTERVENTION

The digital CBT-I program used in this intervention (Somryst) is based off SHUTi , an interactive and tailored English-language web-based program modeled on the primary tenets of face-to-face CBT-I shown to be effective at reducing insomnia symptoms.[26] Participants will be asked to complete six cores (main intervention content) during the 9-week intervention period (a new Core becomes available 7 days after completion of the previous one). After completing a Core, they can review that Core at any time, and access program worksheets from the My Stuff section of the mobile program. The six cores are based on the primary treatment components provided in face-to-face cognitive behavioral therapy for insomnia.[6,14] In order to expand access to the gold standard behavioral treatment for insomnia, adaptations of CBT-I to other languages and cultural contexts is necessary. The digital CBT-I (Somryst) has been adapted using a rigorous cultural adaptation framework. We used Barrera et al.'s cultural adaptation framework[79] to conduct formative qualitative research (N=18) and one-on-one personal interviews (N=13) with Spanish-speaking Latinx adults from the NYC region with chronic insomnia about digital cognitive behavioral therapy for insomnia for funded hybrid Type 1 effectiveness-implementation R01 trial (HS024274). As part of this process, participant input and feedback about sleep hygiene guidelines and ways in which these guidelines could be adapted for their urban context was obtained. Participants identified the need for key deep-level content changes to traditional sleep hygiene education, including adaptations for socioeconomic status and urban settings such as living in multi-generational households, living in apartments and small spaces that required creating separate zones within one room, potential inability to regulate room temperatures, and limited control of noise or light pollution, as well as adaptations to sleep hygiene guidelines for safety concerns. Other important adaptations that were made were related to the salience of immigrant identity, country of origin/heritage group, the importance of family, and adaptations for health literacy and numeracy.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, at least 4 intervention sessions, and the 6-month follow-up assessments.

The end of the study is defined as completion of the 6-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed screening consent form
2. Stated willingness to comply with all study procedures and lifestyle considerations (see **Section 5.3, Lifestyle Considerations**) and availability for the duration of the study (8 months)
3. Males and females; Age 18-65
4. Adults with moderate insomnia symptoms as documented on initial eligibility screen based on validated cut-off for community samples (Insomnia Severity Index Score >10)
5. Willingness to adhere to the digital therapeutic treatment (study-app based intervention) or enhanced usual care study regimen
6. Be Spanish-speaking or bilingual (English and Spanish) adults
7. Self-identify as Hispanic or Latinx
8. Report experience of sleep disturbances for at least 3x/week
9. Report experience of sleep disturbances for at least 3 months

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Participants who are pregnant
2. Participants who are caregivers (e.g., mothers or fathers) of infants (< 3 months of age) or of adults who require care at night
3. Participants who are deemed unable to complete the study protocol as a result of cognitive impairment, severe medical (i.e., unstable epilepsy or seizure disorder, treatment for cancer or congestive heart failure, or a condition that may require hospitalizations, surgery, or new treatments during the study period) or severe mental illness (schizophrenia, psychosis, bipolar I disorder), or active substance use disorder
4. Participation in another treatment or intervention study that would interfere with the current study within the time period beginning from initial baseline assessment until the 6-month follow-up assessment
5. Participation in regular night shift work more than 1x/ week
6. Patients with severe excessive daytime sleepiness ESS>=16
7. Patients with self-reported previous diagnosis of untreated moderate-to-severe obstructive sleep apnea
8. Patients with self-reported or health professional diagnosis of narcolepsy
9. Patients who have received specialty behavioral treatment for insomnia within the past 3 months
10. Change in prescribed depression medications within the past 3 months
11. Change in prescribed insomnia medications (e.g., hypnotics) within the past 1 month, or use of a sedative hypnotic beyond the max therapeutic dose

12. Unavailable for follow-up during the study period (e.g., plan to leave the country for an extended period of time without access to internet)
13. Absence of primary care provider consent for patient participation
14. Patients with non-standard sleep patterns (bedtimes outside of 8pm-2am or awakenings outside of 4am-10am)
15. Patients who have full-time transportation and moving occupations (e.g., full-time motor vehicle operators, drivers [e.g., Ubers, Lyfts, taxis, trucks], pilots)

Children under 18 years will not be included in the study. They will not be included as chronic insomnia is much less common in children than in adults.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Refrain from starting specialty behavioral treatment or pharmacotherapy for insomnia.
- Should not be planning on becoming pregnant in the 8-month duration of the study.
- Remain available during the study period, and as such should refrain from leaving the country for an extended period of time

If a participant has used prohibited medications, if they become pregnant during the study duration, or leave the country for extended periods of time, that will result in early study intervention discontinuation by the study investigator.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include participation in night shift work, pregnancy, change in psychotropic medications for depression in past 3 months or insomnia in past 1 month, caregiving for infant <3 months of age or unavailability during the study period. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

We will enroll 200 Hispanic/Latinx women and men in equal proportion (50% women, 50% men). Participants will be from several racial groups (27% American Indian, 15% Black or African American, and 58% other races or multiple). Participants will be ages 18-65 years old. Participants will be recruited through flyers, email, telephone, and primary care provider referrals from the primary care clinics affiliated with Columbia University Irving Medical Center and New York Presbyterian Hospital (the Ambulatory Care Network) that serves underserved communities across New York City by providing high quality and affordable patient-centered care. Recruitment will be conducted remotely or in person ensuring safety measures are in line with COVID-19 safety guidelines provided by Centers for Disease Control and Prevention and Columbia School of Social Work. All interested patients will complete a standard insomnia questionnaire (the Insomnia Severity Index) to determine study eligibility according to severity of insomnia, and only those patients with a positive insomnia screen who are eligible to participate will be invited for **a remote** study visit, or an in-person visit dependent on participant preference.

For Spanish-speaking patients: We also have developed a range of strategies aimed at racial/ethnic minority patient populations from which we recruit and consent. In particular, we are sensitive to the cultural diversity of our population and appreciative of language barriers, issues that must be addressed for successful recruitment and retention of participants. To accommodate the Hispanic/Latinx community in New York City and the surrounding boroughs, the consent and research participant forms will be in Spanish and written at a 6th grade reading level to ensure suitability across literacy levels. In addition, our hiring practices have been informed by the needs of our population. For our current studies, approximately 75% of our research staff is bilingual and we intend to keep our proportion of Spanish speaking staff at about the same proportion in this project. Hispanic/Latinx participants will be provided with a copy of the consent form and HIPAA form in Spanish. A verbal explanation by a bilingual research member will be provided as well. All ensuing questions will be answered, and participants will then be allowed to sign the consent form and HIPAA form.

Participant incentives

There are no direct benefits to completing the screener. All adult participants have the opportunity to receive up to $180 for their participation depending on which study group they are assigned to. Participants will be informed that they are able to stop participation at any time. The participant incentives are consistent with going rate for study participation in NYC and are not viewed as coercive.

A. Somryst Treatment Group (up to $180 total):
    1. $20 in cash/giftcard for completing the baseline visit
    2. $20 giftcard for wearing the Actiwatch and completing sleep diaries for 14 days at the group assignment visit.
    3. $20 for wearing the Actiwatch and completing sleep diaries for 14 days after treatment is complete.
    4. $40 giftcard for a the post-intervention (9 weeks) telephone call.

5. $80 giftcard for a 6-month telephone call.

B. Minimally enhanced usual care (up to $180 total):
   1. $20 in cash/giftcard for completing the baseline visit
   2. $20 giftcard for wearing the Actiwatch and completing sleep diaries for 14 days at the group assignment visit.
   3. $20 giftcard for wearing the Actiwatch and completing sleep diaries for 14 days after treatment is complete.
   4. $40 giftcard for a post-intervention (9 weeks) telephone call.
   5. $80 giftcard for a 6-month telephone call.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Intervention Arm: digital CBT-I (Somryst), usual care, and sleep hygiene brochure.
Patients who are randomized to Somryst will receive the Spanish-language version of the culturally adapted Somryst, a self-guided digital program of CBT-I, the usual care provided by their PCP, and a sleep hygiene brochure. Somryst, is an interactive and tailored mobile-based program modeled on the primary tenets of face-to-face CBT-I, the web version has been shown to be effective at reducing insomnia symptoms.[25,26]

Patients will be asked to complete six cores (main intervention content) during the 9-week intervention period (a new Core becomes available 7 days after completion of the previous one). After completing a Core, they can review that Core at any time, and access program worksheets from the My Stuff section of the mobile program (App).

The six cores are based on the primary treatment components provided in face-to-face cognitive behavioral therapy for insomnia.[6,14] The Behavioral Cores incorporate sleep restriction and stimulus control, providing patients with a variety of "rules" to follow in order to retrain their bodies to associate sleep with bed. Stimulus control aims to reduce the anxiety or conditioned arousal individuals may feel when attempting to go to bed. Sleep restriction is a form of systematic mild sleep deprivation in which a sleep window is maintained to allow the body to relearn proper sleeping dynamics and increase sleep efficiency. The Educational Core (also called Sleep Hygiene) focuses on general education about sleep (e.g., understanding the different types of sleep problems) and improving sleep hygiene and other maladaptive behaviors (e.g., establishing regular sleeping schedules, eliminating napping, and avoiding nicotine, caffeine, exercise, and drinking alcohol before bedtime). The Cognitive Core (also called Cognitive Restructuring) attempts to address and change the negative beliefs and thoughts about sleep

that may exacerbate sleep difficulties. In addition to these main Cores, there are two other Cores: the Overview and Consolidation/Relapse Prevention Cores. These are critical for each user to receive in order to introduce intervention content and provide a rationale for the intervention (Overview); and integrate the educational, behavioral, and cognitive elements, promote adherence, generalize the information, help the user identify risk situations, and incorporate strategies to reduce relapse (Relapse Prevention).

Somryst relies on user-entered online Sleep Diaries to track progress and to tailor treatment recommendations (i.e., assign a "sleep restriction" window). Intervention content is enhanced through a variety of interactive features, including personalized goal-setting, graphical feedback based on inputted symptoms, animations/illustrations to enhance comprehension, quizzes to test user knowledge, patient vignettes, and video-based expert explanation.

The primary outcome, insomnia symptoms, will be assessed using the ISI at baseline, at post-intervention (9 weeks), and at a 6-month follow-up. Health-related quality of life, sleep quality, secondary outcomes, will also be assessed at the same endpoints as ISI. Daytime sleepiness, another secondary outcome will also be assessed at baseline and at the post-intervention (9 weeks), and 6-month follow-up visit. Satisfaction with care and sleep quality will be assessed at baseline and at post-intervention (9 weeks) and 6-months, and sleep duration and efficiency will be assessed 14 days prior to randomization and at post-intervention (9 -weeks).

Comparator Arm: minimally Enhanced Usual Care (mEUC)- (usual care + sleep hygiene brochure)
Patients randomized to the mEUC condition will continue to receive the typical standard of care in that clinic from their primary care provider (which may include pharmacotherapy). We have labeled the condition "minimally enhanced" because patients will be provided with a sleep hygiene brochure. Minimally EUC was chosen as the comparator because it is of high clinical relevance, will allow us to determine if the adapted digital CBT-I is superior to usual care, and addresses ethical issues (i.e., identifying but not treating insomnia).[78] Patients randomized to mEUC will complete assessments on the same schedule as those randomized to the intervention arm.

6.1.2 ADMINISTRATION AND/OR DOSING

Somryst is self-guided as it is a mobile or digital program. Intervention content is metered out over time through 6 "Cores:" psychoeducation, sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relapse prevention. Users obtain access to a new Core 7 days after completion of previous Core. Participants will complete the program in 6-9 weeks. A Core is expected to take 45 – 60 minutes to review online. Reviewing and implementing program recommendations will take most participants 30 – 45 minutes per week. Thus, in total, participants in the Somryst group should expect a time commitment of up to 12 hours, total. Somryst relies on user-entered online daily Sleep Diaries to track progress and to tailor treatment recommendations (i.e., assign a "sleep restriction" window). A complete dose is considered completion of 6 cores. We will also collect information about number of sleep diaries completed, number of notifications sent, number of days to complete intervention.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Because Somryst is self-guided and delivered completely via mobile App, fidelity to the intervention content will be 100% since there are no interventionists. Study personnel will train participants on the use of Somryst via a virtual Zoom meeting at the randomization visit. A checklist for the training session will be developed for study personnel which will include a standard set of app functions to review such as how to sign on and off of the app, how to navigate the app, and where to find help information on the app. Study videos related to downloading the app and completing sleep diaries will be available to participants and posted on the study website.

Protocol compliance will be reviewed during weekly meetings between Dr. Alcantara, TBN (Project Coordinator) and the research assistants, as well as at monthly meetings (more frequent if required) between Dr. Alcantara and the other co-Is (Drs. Kronish, Schwartz, Moise). Finally, the Project Coordinator will perform a random audit of 5% of study visits, and provide continual feedback to improve the quality of informed consent and data collection.

We have a number of strategies to ensure the quality of the data. First, the web-based electronic data entry system we will use "forces" responses to most questionnaire items before allowing progression through the particular interview's template, thereby avoiding problems with missing data. For some items, delayed data entry is possible. Further, each time the research coordinator logs into the secure data entry system, it prompts pop up on the initial screen showing what data elements remain incomplete, to encourage complete data capture. After enrollment of the first 5 participants, the Steering Committee, led by PI Dr. Alcantara will examine the data to ensure adequacy and accuracy of data collection. Finally, as mentioned above, the DSMB will also review data completeness, accuracy, and timeliness.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization. After completing the baseline assessment, patients will be randomly assigned in a 1:1 ratio to either the Culturally Adapted Somryst or minimally Enhanced Usual Care (mEUC) condition. Randomization will be generated by a computerized random-number sequence programmed by the study statistician and implemented in the secure, password-protected, encrypted data tracking program. The sequence will be unknown to research assistants enrolling patients.

Blinding. One research staff member (TBN) will be responsible for randomizing participants and so this research assistant and the PI will be unblinded to study condition. Participants will also be unblinded to study condition since treatment conditions will be obvious to them. Research assistants conducting the post-intervention (9 weeks) and 6-month outcome assessments will be blinded to participants' treatment condition, as this is preferred to minimize risk of bias in outcome ascertainment.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participants will be asked to complete daily sleep diaries and weekly Cores (6 total) over a 9-week (63 days) period. Research staff will receive weekly information about participant engagement with the digital treatment, including number of log-ins, number of minutes to complete core, number of sleep diaries completed, and time elapsed since completion of core. In the event that participants have not started the App, a notification reminder is sent every day for 8 days. Also, periodic notifications are sent after a set period of non-activity. Please see Appendix of Administrative forms for example notification log.

6.5 CONCOMITANT THERAPY

For this protocol, participants may not begin any specialized behavioral treatment or pharmacotherapy for insomnia for the duration of the study.

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a participant discontinues from Somryst but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation from the study will be recorded on the Case Report Form (CRF) accessed through the data management platform. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the clinic/virtual meeting for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within 14 days, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and texts, if necessary, a certified letter to the participant's last known mailing address, email, or local equivalent methods). These contact attempts will be documented in the participant's study file.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Overview:

NIH Protocol Template for Behavioral and Social Sciences Research

Study candidates who meet initial eligibility criteria and consent to participate will be invited for an office visit or a virtual visit where they will complete a baseline sociodemographic and psychosocial survey battery, and be asked to complete a daily sleep diary for 14 days and to wear an actigraph (Actiwatch) to capture continuous objective sleep data on sleep duration and sleep efficiency for 14 days. Participants will be asked to return their actiwatch via mail. After completing the baseline assessment, patients will be randomly assigned in a 1:1 ratio to either the Culturally Adapted Somryst intervention condition or to minimally Enhanced Usual Care (mEUC) condition. Patients in the intervention group receive digital CBT-I, usual care, and a sleep hygiene brochure. Patients will also be trained on how to record their daily sleep diaries using a smartphone diary; and will receive prompts on their smartphones or emails to remind them when to complete the daily sleep diaries. Patients randomized to the control group will receive minimally enhanced usual care, which will include usual care provided by their PCP and a sleep hygiene brochure. Patients in both groups will have their insomnia severity assessed again at a post-intervention (9 weeks) and 6-months. Patients in both groups will also wear the ActiwatchSpectrum Pro to objectively assess sleep for 2 weeks after enrollment and again for 2 weeks post-intervention (9 weeks).

All study surveys will be administered by research staff remotely via a teleconference platform or in-person dependent on participant preference.

Screening & Primary Endpoint:
All interested patients will complete a standard screening questionnaire to determine study eligibility according to severity of insomnia. Basic sociodemographic and technological literacy information will be collected. Insomnia symptoms in the past 2 weeks will be measured with the Insomnia-Severity Index (ISI) in order to assess severity of insomnia.[80] The ISI has excellent psychometric properties, and is reliable and valid in English,[80] and adapted for use in Spanish-speaking populations.[81] Changes in insomnia symptoms will also serve as the primary outcome.

Baseline:
Study candidates who meet initial eligibility criteria and consent to participate will be invited to a virtual online visit where they will complete a baseline sociodemographic and psychosocial survey battery.

Secondary Outcomes:
Health-related quality of life will be assessed through the validated Short-Form 12 (SF-12), which is a 12-item self-report inventory that generically measures quality of life; it yields a measure of global health-related wellbeing as 8 domain-specific subscores.[82] This will be assessed at baseline and at post-intervention (9 weeks) and 6-month follow-up.

Sleepiness will be measured with the 8-item Epworth Sleepiness Scale, a brief, validated self-report scale of daytime sleepiness with excellent psychometric properties.[83] This will be assessed at baseline and at post-intervention (9 weeks) and 6-month follow-up.

Satisfaction with care will be measured using a question adapted for this trial asking patients to rate the quality of professional care they have received for their symptoms of insomnia.[84] This will be assessed at baseline and at the post-intervention visit (9 weeks). Based on current best practices[66] of cultural adaptation of evidence-based interventions, we will also ask participants in the intervention group to

rate their satisfaction with, as well as their difficulties with program content or activities after each online session.

Self-reported and actigraphy assessed wake after sleep onset and self-reported sleep onset latency will be assessed at baseline and at post-intervention for 14 days.

Sleep duration and sleep efficiency will be measured continuously and unobtrusively for 14 days following the baseline visit and post-intervention using the ActiWatch SpectrumPRO, a waterproof, lightweight, actigraphy-based device that measures physical activity continuously and can be worn for 24 hours daily. The validity of actigraphy for determining sleep duration in particular, compared with the gold standard polysomnography, is excellent.[85]

Sleep quality will be measured at baseline, post-intervention, and at 6-months follow-up with The Pittsburgh Sleep Quality Index (PSQI),[86] which has excellent psychometric properties, and established validity among Spanish-speakers.[87]

Other Measures: ***Sociodemographic Information*** will be collected at screening including, age, sex, race, country of origin, educational attainment, nativity status, household income, employment status, and health insurance status. **Direct health care costs** will consist of the retail costs of Somryst (payer's costs plus patient out-of-pocket costs). Structured interviews will gather information about health care utilization (primary care, other ambulatory care, emergency department, or hospital visits). **Indirect costs** will include patients' lost productivity due to 1) participating in Somryst sessions, and 2) lost productivity related to poor sleep quality.

8.2 SAFETY ASSESSMENTS

Safety assessments will include inquiries into experience of adverse events through semi-structured interviews during the post-intervention (9 weeks) and 6-month assessments. There will also be a creation of a Data Safety and Monitoring Board that will monitor and review adverse events and safety.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

An adverse event will be defined as any undesirable symptom, accident, or medical condition considered related or possibly related to the intervention. Medical conditions present before the intervention will be considered adverse events only if they worsen after starting the study and that

worsening is considered to be related to the study intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse event: The adverse event will be deemed serious if it is determined to be associated or possibly associated with study involvement, and results in any of the following outcomes: death, a life-threatening adverse experience, in-subject hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- No adverse event or within normal limits
- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".
- Life-threatening or disabling adverse event
- Fatal adverse event

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician (PI and study physician Co-I) based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.3.3 EXPECTEDNESS

A clinician (general internist) with appropriate expertise in insomnia will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

Anticipated or expected adverse events will include: initial discomfort/embarrassment from discussion of topics of a sensitive nature or wearing the actigraph, initial tiredness/fatigue from the sleep restriction component of the intervention, and participant confidentiality and privacy concerns about sharing personal information on a digital platform.

Potentially intervention related serious adverse events will include fatigue-related accidents (motor vehicle accidents, work-related accidents).

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.
Research Staff will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Any adverse event (AE) or unanticipated problem will be identified, responded to, recorded by the PI. If the AE or problem is unexpected, related to study involvement, and puts the participant at increased risk, it will be reported to the Columbia IRB immediately, in accordance with local policies, in addition to the Data Safety and Monitoring Board (DSMB) and if necessary, AHRQ. All other AEs and problems will be reported at the time of continuing renewal.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team (study physicians, Moise, Kronish) will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such

evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event

8.3.7 REPORTING EVENTS TO PARTICIPANTS

The PI and study team will follow DSMB guidance regarding reporting of adverse events to participants.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

Pregnancy is not reported as an adverse event. In the event of a pregnancy during trial participant, participants will be asked to discontinue the study intervention.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- 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.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Safety and Monitoring Board/AHRQ. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the Data Safety and Monitoring Board/AHRQ immediately within 24 hours of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within 14 days of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 days of the IRB's receipt of the report of the problem from the investigator

These policies are informed by *https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-adverse-event-and-unanticipated-problem-reporting-policy*.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

The PI and study team will follow DSMB guidance regarding reporting of unanticipated problems to participants.

9 STATISTICAL CONSIDERATIONS

We will post or pre-register our planned analysis plan in clinicaltrials.gov. Information will be provided on the analysis plan for the primary endpoint.

9.1 STATISTICAL HYPOTHESES

[Primary endpoint] Our primary hypothesis is that patients randomized to the Somryst treatment will experience a greater improvement (from baseline) in the Insomnia Severity Index (ISI) at post-intervention (9 weeks) compared to those randomized to mEUC, and scores will continue to be better

than mEUC patients at 6 months post-intervention. The null hypothesis is that there will be no difference in the ISI scores between patients randomized to the Somryst treatment versus those assigned mEUC.

[Secondary endpoints] Our secondary hypothesis is that Somryst will result in greater improvement in quality of life, as captured by the more general SF-12 that will be assessed pre- and post-intervention in both the Somryst and mEUC participants. We will use the validated method of Brazier et al. to calculate utilities (QALY penalties) from baseline and post-intervention (9 weeks) SF-12 data by first mapping responses to the simpler SF-6D scale and then using a regression model to estimate single index scores.[92, 108] Additionally patients in the Somryst treatment will exhibit greater improvement in scores for self-reported daytime sleepiness, satisfaction with care, actigraphy-assessed sleep duration and actigraphy-assessed sleep efficiency, and self-reported sleep quality compared to mEUC patients.

9.2 SAMPLE SIZE DETERMINATION

Prior studies suggest that CBT-I yields approximately an 8-point reduction in the ISI, our primary measure of insomnia, with the standard deviation (SD) of post-intervention change scores being 4 to 5 points. Our expectation is that the improvement in patients assigned to the intervention condition (Somryst) will be 8 points or greater, and that those assigned to minimally enhanced usual care (mEUC) will exhibit a 5-point improvement. Typically, we expect the SD of change scores to increase for longer intervals (e.g., 6 or 12 months), and have therefore conservatively based our power calculations on a SD (change) of 6.0. Accordingly, randomization of 200 patients to Somryst versus mEUC (1-to-1 ratio) will provide 90% power to detect a differential reduction (post-intervention and 6-month follow-up) in ISI of 3 points or larger, using a 2-tailed Wald chi-square test of the appropriate contrast. This sample size estimate allows for up to 15% attrition, such that we have baseline data on all 200 patients (collected prior to randomization), but follow-up data on only 170.

9.3 POPULATIONS FOR ANALYSES

All primary analyses will be conducted according to the intent-to-treat principle, with all randomized patients included in the analysis and their group classification (Somryst versus minimally EUC) based on the condition to which they were randomly assigned.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The distributions of all clinical measures will be reviewed for outliers. Those exhibiting substantial skewness will be transformed (e.g., log or square root) to make their distribution more appropriate for parametric procedures. Independent-sample t-tests and chi-square analyses will be used to examine baseline differences between the two treatment groups (Somryst vs. mEUC) in clinical and

sociodemographic characteristics. All primary analyses will be conducted according to the intent-to-treat principle, with all randomized patients included in the analysis and their group classification (Somryst versus mEUC) based on the condition to which they were randomly assigned.
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9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Mixed-model RM-ANOVA will be used to estimate and compare the changes in the primary endpoint (ISI) and other patient-important outcomes (e.g., insomnia symptom severity, daytime sleepiness) between Somryst and mEUC. The RM-ANOVA model will include Group (Somryst versus mEUC), Time (baseline, post-intervention and 6-month follow-up), and the Group × Time interaction as fixed factors with an unstructured residuals covariance matrix. This will yield estimates of the within-group means and standard errors at each assessment. Specific interaction contrasts (e.g., Group × Pre-vs-Post Intervention) will be estimated to estimate the magnitude and test the statistical significance of the differential change in insomnia symptoms using the Wald $\chi 2$ statistic. We will plot the mean insomnia scores across assessments, stratified by treatment group, to elucidate the nature of the interaction (i.e., whether Somryst resulted in significantly greater improvements [or lesser worsening] than mEUC). If, despite randomization, the two groups differ substantially ($p<0.10$ after stepdown Bonferroni correction) on one or more sociodemographic or clinical factors assessed at baseline, sensitivity analyses will be performed in which these factors are included as covariates in the RM-ANOVA, in order to rule out the possibility that the results from the primary analyses are attributable to group differences on these factors. The same analyses will be repeated to estimate and compare changes in the primary endpoint and secondary endpoints between Somryst and mEUC at 6-months.

Significance will be evaluated with a two-tailed p value of 0.05. To control for multiplicity, post-intervention will be evaluated first and if significant timepoints post-intervention and 6-months follow-up will be evaluated. In addition, estimated marginal means ± 95% confidence intervals will be calculated for each assessment point and Cohen's d will be used as an estimate of effect size for the change from baseline to each assessment point.

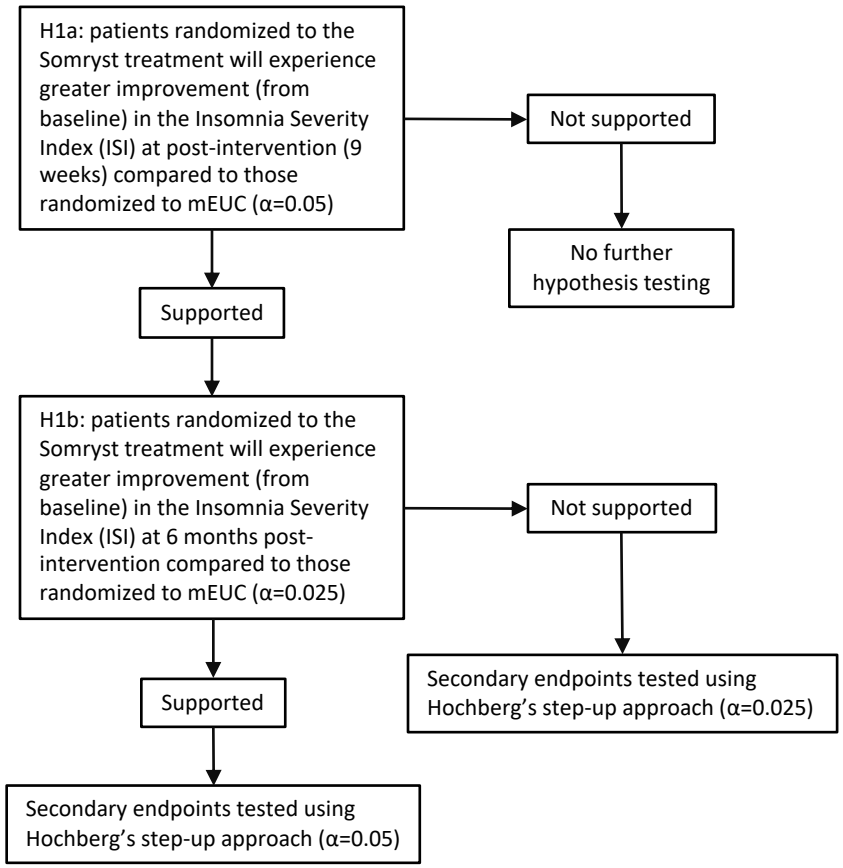
Missing Data: We will use multilevel mixed models to perform intent-to-treat RM-ANOVA. There will be no missing data at baseline, because we will only randomize patients who have successfully completed the baseline assessment, and therefore all 200 patients will be included in the analyses. The software used to estimate the mixed models yields full-information maximum-likelihood parameter estimates that are robust with respect to data that are "missing at random". This will appropriately handle the possibility that attrition (or missing data) is related to either baseline level of the outcome measure, group assignment, or their interaction. However, if we discover that attrition is associated with some other characteristic (e.g., sex or age), we will use multiple imputation (chained equation approach[104, 105]) and include the associated characteristic in the imputation model.[106] We will do everything possible to collect data on the reasons for dropout, who decided the participant should drop out (e.g., their PCP), and whether the dropout involves any aspect of participation in the study. Even if the patient drops out of the intervention, we will still seek to collect their key outcome information. We will compare key characteristics of participants with and without missing data. In cases where there are large differences

in missing data, we will cautiously interpret our findings and will consider limitations in generalizability that might have been introduced by these differences.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For secondary endpoints, , we will follow Hochberg's step-up approach as outlined in Figure 2.

Figure 2. Decision structure for hypothesis testing of primary and secondary endpoints



Coupled with our primary hypothesis that CBT-I will result in improved ISI scores, a secondary hypothesis is that CBT-I will result in *greater improvement in* quality of life, as captured by the more general SF-12 that will be measured pre- and post-intervention in both the CBT-I and mEUC participants. We will use the validated method of Brazier et al. to calculate utilities (QALY penalties) from baseline and post-intervention SF-12 data by first mapping responses to the simpler SF-6D scale and then using a regression model to estimate single index scores.[97, 98] The cost-effectiveness analysis will compare incremental costs and quality-adjusted life years (QALYs) gained in the CBT-I arm compared with mEUC. The primary cost-effectiveness analysis will be from the payer's point of view (government, insurer, or health

organization). The secondary cost-effectiveness analysis will be from the patient's point of view and include out-of-pocket medical costs and costs of lost productivity (both due to participation in Somryst sessions and due to poor sleep quality). For the main analysis from the payer's point of view, we will include cumulative CBT-I costs for the intervention arm payers and patients' combined costs to access and complete the web-based CBT-I intervention), and for both CBT-I and mEUC we will gather cumulative utilization data on medications, office visits, emergency department visits, and hospitalizations over the follow up period. We anticipate that most of these data can be gathered from EPIC the electronic health record (EHR) used in the AIM Clinic and New York Presbyterian Hospital, but participant follow up interviews will both validate electronic record data and capture any health care utilization at outside clinics and hospitals. Health facility visit costs will be entered as the reimbursement for that visit type specified by the Centers for Medicare and Medicaid Services[99] fee schedule. Mean wholesale medication prices will be estimated from the most recent "Redbook" listing of wholesale drug costs. For the secondary analysis from the patient's point of view, we will analyze data from participant interviews data on out-of-pocket medication costs, office visit co-pays, and lost compensation and missed work. Productivity losses will be estimated by multiplying age-specific labor force participation rates by average age-specific U.S. adult annual earnings for the participant's time observed in in the trial. Sources for average annual earnings (Current Population Survey 2014), labor force participation rate (Bureau of Labor Statistics, BLS), and consumption costs (BLS Consumer Expenditure Survey) were summarized in the Second Panel of Cost-Effectiveness.

Cost-effectiveness will be assessed based on the study observation period (9 weeks) in the main analysis, but micro- simulation analyses will simulate sustaining the insomnia prevention effects of CBT-I and EUC for years into the future, up to 10 years. Incremental cost-effectiveness ratios (ICERs) will be calculated as incremental change in costs divided by incremental change in QALYs comparing Somryst to mEUC).). ICERs will be assessed as follows (in 2021 $U.S.): <$50,000 per QALY gained will be considered cost-effective, ≥$50,000 and <$150,000 of intermediate value, and ≥$150,000 of low value. Non-parametric bootstrapping with 1,000 random samples of all QALY and cost distributions will be used to generate 95% uncertainty intervals for cost- effectiveness ratios.[100] Sensitivity analyses will test the robustness of the cost-effectiveness estimate to a range of inputs regarding intervention costs, productivity and quality of life losses related to chronic insomnia, size of quality of life improvement effect, and durability of intervention effect (ranging from one month to ten years). Cost-effectiveness analyses will be carried out and reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[101] Cost-effectiveness analyses will be carried out in TreeAgesoftware (TreeAge Inc., Williamstown, MA)

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Independent-sample t-tests and chi-square analyses will be used to examine baseline differences between the two treatment groups (Somryst vs. mEUC) in clinical and sociodemographic characteristics.

9.4.6 PLANNED INTERIM ANALYSES

N/A.

9.4.7 SUB-GROUP ANALYSES

In secondary analyses, we will repeat the primary analyses stratified by age, gender, nativity status, number of medical comorbidities, socioeconomic status, employment status, language proficiency, psychological profile [depression, anxiety, stress scores. The results (point estimates and 95% confidence intervals) will be displayed in a Forest plot, where marked subgroup differences will be visually evident and used for hypothesis generation about whether one or more of these factors influences treatment response.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

We will also conduct an exploratory analysis of treatment effect modification by baseline comorbidity level, a sensitivity analysis in which those using sleep medications are excluded, and a test of whether there were any group differences in the initiation/use of sleep medications (prescribed or over the counter)

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Patients who are eligible to participate will be invited for a remote or in-person study visit at which we will obtain verbal informed consent after explaining the study and ensuring that patients understand all study components including the nature of their participation, the meaning of randomization, and equipoise between the two arms of the trial. Participants will receive consent form via email or in the mail prior to the remote visit. Participants who attend in-person visits will receive a copy of the consent form. Before consenting patients for the trial, permission for patients' participation will be obtained from their primary care providers (PCPs). Consent and all research participant forms will be translated into Spanish given that this study focuses on the Spanish speaking Hispanic/Latinx community in New York City and the surrounding boroughs. Our research staff is bilingual and will facilitate consent in Spanish with Spanish-speaking participants. All staff involved in this study will have completed and passed GCP and HIPAA training, and will have been provided with materials and instruction in the proper and ethical manner in which consent should be obtained.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, AHRQ, and regulatory

authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

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

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, survey records for the participants in this study. The PI will permit access to such records.

The study participant's contact information will be securely stored on a virtual data management platform for internal use during the study. At the end of the study, all records will continue to be kept in this secure virtual data management platform for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored in an encrypted study laptop. 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 Columbia University research staff will be secured and password protected.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

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