BMJ Open

PreScription DigitaL ThErapEutic for Patients with Insomnia (SLEEP-I): a protocol for a pragmatic randomised controlled trial

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To cite: Dreyer RP, Berkowitz A, Yaggi HK, *et al*. PreScription DigitaL ThErapEutic for Patients with Insomnia (*SLEEP-I*): a protocol for a pragmatic randomised controlled trial. *BMJ Open* 2022;**12**:e062041. doi:10.1136/bmjopen-2022-062041

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-062041).

Received 15 February 2022
Accepted 17 July 2022

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ABSTRACT

Introduction Cognitive behavioural therapy for insomnia (CBT-I) is effective at treating chronic insomnia, yet in-person CBT-I can often be challenging to access. Prior studies have used technology to bridge barriers but have been unable to extensively assess the impact of the digital therapeutic on real-world patient experience and multidimensional outcomes. Among patients with insomnia, our aim is to determine the impact of a prescription digital therapeutic (PDT) (PEAR-003b, FDA-authorised as Somryst; herein called PDT) that provides mobile-delivered CBT-I on patient-reported outcomes (PROs) and healthcare utilisation.

Methods and analysis We are conducting a pragmatically designed, prospective, multicentre randomised controlled trial that leverages Hugo, a unique patient-centred health data-aggregating platform for data collection and patient follow-up from Hugo Health. A total of 100 participants with insomnia from two health centres will be enrolled onto the Hugo Health platform, provided with a linked Fitbit (Inspire 2) to track activity and then randomised 1:1 to receive (or not) the PDT for mobile-delivered CBT-I (Somryst). The primary outcome is a change in the insomnia severity index score from baseline to 9-week postrandomisation. Secondary outcomes include healthcare utilisation, health utility scores and clinical outcomes; change in sleep outcomes as measured with sleep diaries and a change in individual PROs including depressive symptoms, daytime sleepiness, health status, stress and anxiety. For those allocated to the PDT, we will also assess engagement with the PDT.

Ethics and dissemination The Institutional Review Boards at Yale University and the Mayo Clinic have approved the trial protocol. This trial will provide important data to patients, clinicians and policymakers about the impact of the PDT device delivering CBT-I on PROs, clinical outcomes and healthcare utilisation. Findings will be disseminated to participants, presented at professional meetings and published in peer-reviewed journals.

Trial registration number NCT04909229.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Prospective randomised controlled trial is used to examine the impact of using a novel mobile phone-based, prescription digital therapeutic delivering cognitive behavioural therapy for patients with chronic insomnia.
⇒ The strengths of this study include the rigour and reproducibility of the trial design as well as the use of a novel patient-centred health data-aggregating platform (Hugo) for data collection, including healthcare utilisation and patient follow-up.
⇒ Limitations include the homogeneous population recruited from two sleep medicine clinics and reliance on participants motivation to engage in and complete both the sleep diaries and behavioural intervention.

INTRODUCTION

Insomnia is one of the most prevalent health concerns and imposes a significant physical, psychological and financial burden on patients' lives.[1] Up to 50% of the general adult population experience insomnia symptoms, with 12%–20% meeting criteria for chronic insomnia.[2 3] The impact on both the individual and the healthcare system is substantial. Insomnia accounts for over $100 billion of US annual healthcare costs,[4–6] and lost productivity related to insomnia costs the US economy approximately $63 billion a year.[7] Adults suffering from insomnia also have a higher likelihood of comorbid conditions such as depression, resulting in a reduced quality of life and higher rates of morbidity and mortality.[8] The documented high rates and detrimental effects of insomnia and co-occurring disorders, including depression, provide a compelling rationale for identifying effective, accessible, easy-to-use and cost-effective treatments.

There is empirical evidence indicating that cognitive-behavioural therapy for insomnia (CBT-I) can effectively treat chronic insomnia,[9–15] including when present with

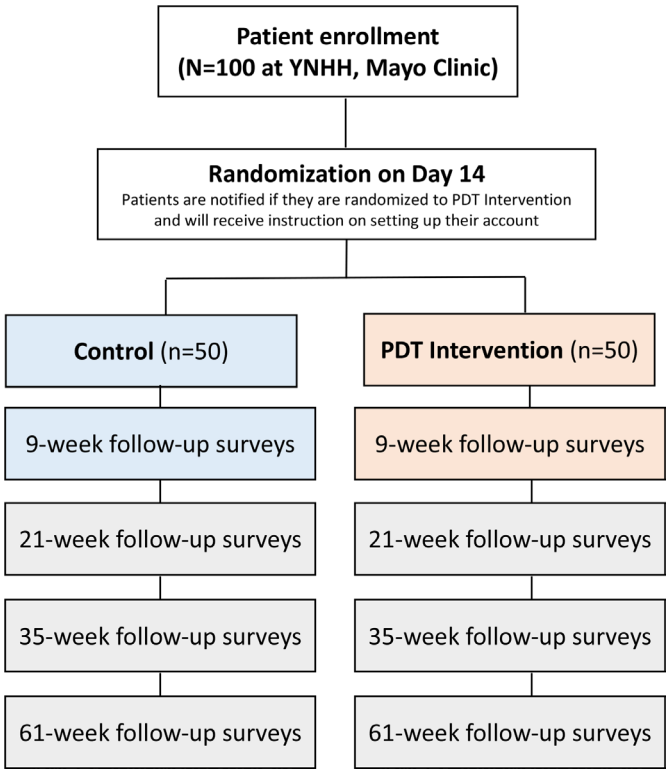

Figure 1 Study design flow of the SLEEP-I study. SLEEP-I, PDT, prescription digital therapeutic; SLEEP-I, PreScription DigitaL ThErapEutic For Patients with Insomnia; YNHH, Yale-New Haven Health.

co-occurring disorders like major depression,[16] with long-lasting benefits. CBT-I is now recommended as first-line therapy for insomnia[15 17] and its primary components include a focus on sleep restriction and consolidation, stimulus control, sleep hygiene and cognitive restructuring.[18] However, due to challenges associated with in-person CBT-I, such as lack of trained clinicians, poor access and limited fidelity,[19] attention has turned towards use of technology to overcome obstacles and deliver CBT-I interventions (eg, Sleep Healthy Using the Internet: SHUTi).[20–23] Despite promising clinical efficacy in randomised controlled trials (RCTs),[23] these studies have been unable to rigorously assess impact of the digital therapeutic on patient experience in the real-world.

In light of this gap in knowledge, we designed the PreScription DigitaL ThErapEutic For Patients with Insomnia (SLEEP-I) trial, a pragmatic, multicentre RCT to collect and evaluate real-world data from a mobile CBT-I prescription digital therapeutic (PEAR-003b, FDA-authorised as Somryst, herein called PDT) for patients with insomnia using Hugo,[24] a patient-centred data aggregating platform. This approach will allow the concurrent analysis of clinical outcomes data, healthcare utilisation data and data from connected devices. The data generated will be used alongside clinically validated measures of insomnia to yield a multidimensional analysis of patient benefit. The PDT will be delivered via mobile devices to patients with insomnia as six treatment core CBT-I modules over 9 weeks that target three common mechanisms of action: stimulus control, sleep restriction and cognitive restructuring.[21 22 25] We will also enrol patients in the Hugo data-aggregating platform to understand patient experience with insomnia by aggregating patients' electronic health record (EHR) data, survey data on patient-reported outcomes (PROs), healthcare utilisation metrics and patient activity recorded via Fitbit.

METHODS AND ANALYSIS

We used the SPRINT reporting guidelines to draft this protocol paper outlining the SLEEP-I clinical trial.[26] Enrolment for the SLEEP-I study was initiated on 22 December 2021 and is projected to be completed by 31 December 2022.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Overall study design and data collection

SLEEP-I is a pragmatically designed, prospective, multicentre RCT using a two group parallel design (PDT vs control) by five assessments (baseline, 9 weeks, 21 weeks, 35 weeks and 61 weeks) to evaluate the impact of the use of the PDT on PROs and clinically validated metrics for insomnia (figure 1). This study leverages a patient-centred health data-aggregating platform called Hugo,[24] which was initially developed to overcome many of the limitations of traditional clinical trials, such as cost and patient access.[27] Using patients' mobile devices or computers, Hugo aggregates electronic health data for each patient from multiple sources, including electronic health records from hospitals and physicians offices, pharmacies and payors along with data from personal digital devices and wearables, by leveraging Blue Button technology and Application Programming Interfaces. Hugo aggregates electronic health data for patients from multiple sources including EHRs (hospitals, physicians offices, clinics), pharmacies, payors and wearables using hl7 fast healthcare interoperability resources and other application programming interface. Hugo also has the capability of delivering patient surveys through emails or text messages which essentially enables the assessment of PROs and other information without face-to-face interaction with study coordinators after enrolment.[24] After the consent process, all participants will be enrolled in the Hugo platform, whereby they will receive near-real time access to their electronic health data from multiple sources, which will be shared with the research team; no data will be directly obtained from healthcare systems.[28] This study will also employ use of the Fitbit (Inspire 2) fitness tracker that integrates with Hugo to obtain multiple physiological and sleep measurements including the number of steps per day, sleep (total sleep time in minutes) and self-reported metrics such as weight, height and body mass index (BMI). We chose to use the Fitbit

Inspire 2 wearable in this study to measure basic activity and sleep metrics due as their affordability, unobtrusive nature and ease of linkage with mobile devices. In terms of reliability, prior work has demonstrated a high inter-device reliability for steps, distance, energy expenditure and sleep duration for certain Fitbit models. Importantly, for patients wearing the wrist Fitbit overnight, there was almost perfect levels of agreement (96.5%–99.1%) to classify whether the minute-level data were sleep or wake.[29 30] That said, sleep diaries and the insomnia severity index (ISI) will form the gold-standard metric for insomnia assessment and the activity tracker will serve as an exploratory variable.

Sample selection and screening

Participants will be recruited from two academic health systems: Yale-New Haven Health (YNHH) and the Mayo Clinic. Potential participants with insomnia will be seen initially by a sleep provider at the YNHH and Mayo Sleep Centers to confirm a diagnosis of insomnia based on the International Classification of Sleep Disorders, 3rd edition,[31 32] and if eligible, will introduce patients to the Sleep-I study. Participants will then be approached by a study coordinator using both in person and virtual recruitment methods via a referral from a sleep provider. Study flyers will also be used across both sleep centres to advertise the study and allow eligible patients to directly contact the study coordinators. Additional recruitment pathways may be employed to capture patients if enrolment targets are not initially met (eg, recruitment from psychiatry/stress centres, retrospective review of medical charts for recently diagnosed patients, social media outreach). Eligible patients will be consented by the study coordinator, and on enrolment, patients will be asked to sign an electronic consent at YNHH (online supplemental file 1) and the Mayo Clinic (online supplemental file 2) as well as linking their electronic health records and Fitbit to Hugo. All participants will receive paper materials on sleep hygiene and healthy sleep tips, which include behavioural information regarding getting a good night's sleep (eg, setting a regular bedtime, getting out of bed if remaining awake, exercising regularly, not smoking). Participants randomised to PDT will receive access to the therapeutic for 9 weeks in addition to the sleep hygiene material.

Inclusion/exclusion criteria

Inclusion criteria will be confirmed prior to the informed consent process. Patients who do not meet all inclusion criteria or meet any of the non-inclusion criteria will not proceed with consent and enrolment. Patients must fulfil the following criteria prior to trial enrolment: (1) aged between 22 and 64 years; (2) English-speaking (both reading and writing in English required) and (3) have a diagnosis of chronic insomnia. Additionally, participants must also be willing and able to give consent to participate in the study, to have an email account (or be willing to create one), to have a smartphone capable of downloading the necessary applications and willing and able to use the PDT, the Hugo data aggregating platform and the syncable device (eg, Fitbit).

Exclusion criteria will include: (1) pregnancy; (2) shift work or family/other commitments that interfere with the establishment of regular night-time sleep patterns; (3) if wake/sleep time is outside the ranges of 4:00–10:00 hours (wake time) and 20:00–02:00 hours (bedtime), respectively; (4) absence of reliable internet access and smartphone; (5) a reported diagnosis of psychosis, schizophrenia or bipolar disorder or any medical disorders contraindicated with sleep restriction (eg, individuals with unstable or untreated medical or psychiatric conditions, specifically bipolar disorder and seizure disorder); (6) current involvement in a non-medication treatment programme for insomnia (participants are still eligible if they are taking traditional sleep medications) and (7) those with untreated coexisting sleep conditions (eg, sleep apnea) and those who have failed CBT-I in the past.

Intervention and method of assignment/randomisation

After signing informed consent documentation, participants will complete their baseline questionnaires and, over the following 2 weeks, will complete their baseline sleep diaries. Patients will be randomised 1:1 to the PDT or the control arm using a randomisation algorithm via Hugo. A total of 100 participants with chronic insomnia from two health centres (50 at each site) will be enrolled in Hugo, provided with a linked Fitbit (Inspire 2) to track activity and then randomised 1:1 to receive (or not) the PDT for mobile-delivered CBT-I. Patients will be notified if they are randomised to the treatment arm on day 14 by the study coordinators and will be provided with instructions on how to set up and create their PDT account if randomised to the PDT arm. The study will not employ blinding as patients will need to know if they are completing the PDT-delivered treatment.

The treatment duration will be 9 weeks, and there will be a 21-week, 35-week and 61-week follow-up. All patients will be evaluated at baseline, as well as prompted to complete additional assessments at weeks 9-week, 21-week, 35-week and 61-week postrandomisation (figure 1). The PDT intervention will deliver CBT-I via mobile devices as six treatment core modules over 9 weeks. Using the Hugo platform, we will also collect patient-generated engagement data, healthcare utilisation and patient activity/clinical outcomes for patients with insomnia.

Patients will use their own mobile devices but will be given the necessary syncable devices to keep (ie, Fitbit Inspire 2) and will receive a stipend for their time contributed as part of this study. This stipend will cover the consent process, initial setup and baseline questionnaire (3 hours), questionnaires provided at 9-week, 21-week, 35-week and 61-week postrandomisation, and the time it takes to sync and use the provided devices (3 hours per timepoint).

CBT-I intervention description

The intervention is the FDA-market-cleared PDT (Somryst) that delivers digital CBT-I via a mobile device that addresses maladaptive behaviours, dysfunctional thoughts and routines that can perpetuate sleep problems. Digital CBT-I is modelled on face-to-face CBT-I, which is usually delivered in weekly sessions over a period of 6–8 weeks. The intervention in this study delivers six treatment Cores (learning modules) that cover various specific CBT-I therapy content which has been previously described in detail.[33 34] Cores of the PDT are completed sequentially and take approximately 30–45 min to complete. Each new Core is made available 1 week after the completion of the previous Core. Between Cores 1 and 2, at least five daily sleep diaries (integrated into the programme) within a 7-day period must also be entered to unlock the next Core. Furthermore, the participant must complete five out of seven sleep diaries between each Core in order to receive an updated Sleep Window. The digital therapeutic uses the Consensus Sleep Diary as recommended by the expert consensus panel which has been previously described.[35] Participants will have access to the programme for 9 weeks, after which time their access will be expired. Although all Cores can be completed in as little as 6 weeks, the intervention will be available for 9 weeks prior to postassessment to allow users sufficient time to access all Core materials, as well as implement new behaviours, strategies and techniques.[33 34]

Sociodemographic and clinical characteristics

Baseline characteristics including sociodemographic, socioeconomic status, risk factors, comorbidities and sleep characteristics will be collected via self-report through Hugo at enrolment (table 1). Patients will also self-report the use of over-the-counter medications, including medications to assist with sleep and/or insomnia.

Outcome measures

The primary, secondary and exploratory study outcomes, including the timing of data collection/administration of measures collected through Hugo and Fitbit, are presented in table 2. PROs collected in this study include the ISI score,[36] the Epworth Sleepiness Scale (ESS),[37] the Patient Health Questionnaire-8 (PHQ-8),[38] the Generalized Anxiety Disorder-7 (GAD-7),[39] the Perceived Stress Scale (PSS-10)[40] and the Short-Form-12 (SF-12).[41]

The primary outcome is a change in the ISI score[36] from baseline to 9-week postrandomisation. The ISI questionnaire is a 7-item global index of self-reported insomnia symptom severity that has been shown to be valid, reliable and sensitive to changes in insomnia treatment[36 42] and validated for online use.[43]

The secondary outcomes will be ascertained at baseline, 9-week, 21-week, 35-week and 61-week postrandomisation: (1) healthcare utilisation outcomes data available in patients' electronic medical records (EMRs) through Hugo, which may include the number of outpatient visits and specialty care visits, number of medication refills for sleep and psychotropic medications, comparing PDT to control at all follow-up time points (9 weeks, 21 weeks, 35 weeks and 61 weeks); (2) change from baseline to 21, 35 and 61 weeks in the ISI, comparing PDT to control and (3) change from baseline to 9-week, 21-week, 35-week and 61-week postrandomisation in individual PROs including daytime sleepiness (ESS),[37] depressive symptoms (PHQ-8),[38] anxiety (GAD-7),[39] stress (PSS-10)[40] and health status (SF-12),[41] comparing PDT to control. The ESS is the most widely used tool for measuring daytime sleepiness for clinical and research purposes.[44 45] It is a simple, self-administered, eight-item questionnaire that measures the risk of falling asleep in eight specific situations that are commonly met. A score of less than 10 is considered normal. The higher the score (from 10 to 24), the greater the reported subjective daytime sleepiness.[37]

Table 1 Sociodemographic and clinical variables obtained at baseline from self-report

Sociodemographics/ socioeconomic status	Risk factors	Comorbidities	Sleep history
Age	Hypertension	Alcohol use	Sleep difficulties
Sex	Diabetes	Coronary heart disease	Insomnia treatments
Race/ethnicity	High cholesterol	A heart attack (also called myocardial infarction)	Length of sleep problems
Marital status	Smoking history	Cancer	
Employment/working status		Depression	
Education status		PTSD	
Annual income level		General anxiety disorder	
		Stroke/TIA	
		Chronic pain	
		Asthma or lung problems	

PTSD, post-traumatic stress disorder; TIA, transient ischaemic attack.

Table 2 Primary, secondary and exploratory outcomes

	Weeks				
	Enrolment (baseline)	9W	21W	35W	61W
Primary outcome					
ISI score (change in ISI from baseline to 9-week postrandomisation)		x			
Secondary outcomes					
Patient-reported outcomes (Hugo)					
ISI score	x		x	x	x
ESS	x	x	x	x	x
PHQ-8	x	x	x	x	x
GAD-7	x	x	x	x	x
PSS-10	x	x	x	x	x
SF-12	x	x	x	x	x
Healthcare utilisation outcomes (Hugo)					
No. outpatient visits		x	x	x	x
No specialty care visits		x	x	x	x
No. medication refills for sleep		x	x	x	x
No. of medication refills for psychotropic medications		x	x	x	x
Health Utility Scores (Hugo)					
Health utility scores (SF-12)		x	x	x	x
Sleep diaries*					
SE	x	x	x	x	x
SOL (min)	x	x	x	x	x
WASO (min)	x	x	x	x	x
Number of awakenings	x	x	x	x	x
Sleep quality (scale score)	x	x	x	x	x
Time in bed	x	x	x	x	x
Total sleep time	x	x	x	x	x
Exploratory outcomes (FitBit feature comparisons)					
Steps per day	x	x	x	x	x
Sleep (total sleep time in minutes)	x	x	x	x	x
Weight	x	x	x	x	x
Height	x	x	x	x	x
Body mass index	x	x	x	x	x

*Definition of key sleep outcomes:
SE: The ratio of TST to TIB.
SOL: The length of time that it takes between 'lights out' or intention to sleep and first onset of sleep.
Sleep quality: One's satisfaction of the sleep experience, integrating aspects of sleep initiation, sleep maintenance, sleep quantity, and refreshment on awakening.
WASO: Total time awake between initial sleep onset and final morning awakening.
ESS, Epworth Sleepiness Scale; GAD-7, Generalized Anxiety Disorder-7; ISI, insomnia severity index; PHQ-8, Patient Health Questionnaire-8; PSS, Perceived Stress Scale; SE, sleep efficiency; SF, Short-Form; SOL, sleep onset latency; TIB, time in bed; TST, total sleep time; WASO, waking after sleep onset.

The PHQ-8 is a measure of depressive symptoms in the general population.[46] Participants indicate the frequency with which they have been bothered by eight depressive symptoms (eg, 'little interest or pleasure in doing things') in the prior 2 weeks. Response options range from 0 (not at all) to 3 (nearly every day) and are summed to create the total symptom severity score. The GAD-7 is a validated screening tool and measure of severity of generalised anxiety disorder[39] and contains seven items, with each response ranked from 0 (not at all sure) to 3 (nearly every day). A GAD-7 of 0–4 indicates minimal anxiety, of 5–9 indicates mild anxiety, 10–14 indicates moderate anxiety and of 15+ indicates severe anxiety.[47]

The PSS-10 is a global perceived stress scale where respondents are evaluated on the degree to which they perceived their life situations over the past month to be unpredictable, uncontrollable or overloaded, with higher scores indicating greater stress. Last, the SF-12 instrument measures overall physical and mental health status through 12 items.[41] Both the Physical Component Summary and Mental Component Summary scores were used for this study and range from 0 to 100, with higher scores indicating a greater level of physical or mental functioning.

Asides from PROs administered in this study, additional secondary outcomes include: (1) Change in sleep outcomes collected through sleep diaries (sleep efficiency, sleep onset latency (SOL) (minutes), waking after sleep onset (WASO) (minutes), number of awakenings, sleep quality (scale score), time in bed and total sleep time, from baseline to 9-week, 21-week, 35-week and 61-week postrandomisation comparing PDT to control. Following the baseline assessment that will include questionnaires as described above, patients will complete 10 days of sleep diaries within a 14-day window as well as at all follow-up time periods. The sleep diaries are part of recent guidelines from the American Academy of Sleep Medicine[17 48] as outcomes to be considered in evaluation of efficacy and clinical significance. Other secondary outcomes will include; (2) Change in (and total) health utility scores using the SF-12 among patients randomised to receive PDT versus the control only at 9-week, 21-week, 35-week and 61-week postrandomisation. Last, for patients randomised to the PDT, we will examine the relationship between engagement with the PDT and clinical outcomes, particularly the sleep-specific outcomes (ISI and diary-derived sleep metrics). More specifically, engagement will be operationalised by evaluating engagement and adherence rates with the PDT findings from the in-therapeutic software application data including: (1) core completion rates and (2) intervention sleep diary completion rates. Other variables will also be explored, including number of times the PDT is logged into/opened.

The exploratory outcomes will be ascertained at 9-week, 21-week, 35-week and 61-week postrandomisation. Physical and sleep activity measured using Fitbit (steps per day, sleep (total sleep time in minutes) and self-reported metrics such as weight, height and BMI from baseline to 9-week, 21-week, 35-week and 61-week postrandomisation comparing PDT to control.

Data analysis plan

All analyses of results from this RCT will be conducted as intent-to-treat to avoid the effects of crossover and dropout.[49] We will report baseline descriptive statistics for the overall study, by site, and for both the control and treatment arms of the study. Baseline data will be compared using Pearson χ^2 tests or Fisher exact tests for dichotomous and/or categorical variables and student's t-tests for continuous variables. If variables are deemed as non-parametric, we will use a median test such as a Mann-Whitney *U*-test, where appropriate.

For the primary outcome, we will use a *t*-test to compare the ISI scores[36] for the intervention (PDT+Fitbit) and control group (Fitbit only) at baseline. We will then use a 2 (group)×2 (time) repeated measures analysis of variance (RM ANOVAs) to compare prechanges to postchanges from baseline to 9 weeks across groups.[21 25] Paired sample *t* tests by group will be used to examine time effects within each condition (if the overall interaction effect is significant). At weeks 21, 35 and 61 postrandomisation, we will also perform the same analysis, but this will be as an exploratory secondary endpoint. If a patient drops out, we will carry forward the most recent PRO response. As this is an RCT, we expect that confounding will be minimal. If patients are missing outcome data, we will use the last observation carried forward for the patient-reported outcome. Missing covariates will be set to missing.

For the secondary outcomes using the PROs, we will calculate the change in the ESS,[37] PHQ-8,[38] GAD-7,[7] PSS-10[40] and SF-12,[41] and the scores at baseline and at 9-week, 21-week, 35-week and 61-week postrandomisation and perform a comparison between patients randomised to the intervention (PDT+Fitbit) and patients randomised to the control (Fitbit only). Based on our prior work using SHUTi,[50] we will examine the change in scores between groups using a mixed model repeated measures ANOVA[51] with an unstructured matrix and estimated df with Satterthwaite's correction. We will present df alongside F-test statistics and t statistics. For the secondary clinical/healthcare utilisation outcomes, we will compare the PDT to the control at all follow-up time points. These comparisons will be compared using *t*-tests at each time point.

For the sleep diary outcomes,[21] we will calculate the change in each sleep outcome from baseline to 9-week, 21-week, 35-week and 61-week postrandomisation comparing PDT to the control based on sleep diaries. We will examine the change in scores between groups using a mixed model repeated measures ANOVA.[51] Paired-sample *t*-tests will be used to examine time effects within each condition if the overall interaction effect is significant.

For the secondary health utilities outcome, we will calculate the change in health utility scores from baseline to 9-week, 21-week, 35-week and 61-week postrandomisation and perform a comparison between patients randomised to the intervention (PDT+Fitbit) and patients randomised to the control (Fitbit only). Health utilities scores are derived from the SF-6D algorithm as applied to the SF-12 data.[52]

For the secondary engagement outcome, we will examine the relationship between engagement with PDT and clinical outcomes in the PDT arm at all follow-up time points. Correlations between engagement and clinical outcomes will be evaluated using both Pearson's correlation coefficient and Spearman's rank correlation as follows. Change from baseline (follow-up–baseline)

will be calculated for ISI, sleep diary-derived metrics of SOL and WASO and PHQ-8, at both the end of treatment and the end of all follow-ups. These will be correlated with core completion rates, sleep diary completion rate and the number of times the PDT is opened. In addition, clinical outcomes among those who complete all six cores of treatment will be examined.

Last, the exploratory physical and sleep activity outcomes (measured using Fitbit) will again be compared from baseline to 9 weeks, 21 weeks, 35 weeks and 61 weeks comparing PDT to control. We will examine the change in scores between groups using a mixed model repeated measures ANOVA.[51] Paired-sample *t*-tests will be used to examine time effects within each condition if the overall interaction effect is significant. We will use a Bonferroni correction to adjust for an increased likelihood of a type I error due to multiple comparisons. A value of $p<0.05$ will be considered statistically significant. All analyses will be conducted in SAS (V.9.4) and performed at the Mayo Clinic.

Sample size calculation

Our sample size was determined assuming 90% power to detect an effect size of d=0.52 for the main outcome (change in ISI from baseline to 9-week postrandomisation),[50] with alpha 0.05 using the PASS software (PASS 15) to detect a clinically meaningful change.[53] This effect size is 1/2 to 1/3 of what we have seen previously. Because this effect size is smaller than the levels demonstrated in RCTs, we are adequately powered to detect changes of interest in the main ISI outcome. We further note that this calculation is conservative because the analysis may optionally draw from outcome values recorded at baseline and each follow-up time. Because the models assume that each outcome is normally distributed, the outcome effects represent the average amount each outcome is expected to change with the incremental shift in any explanatory variable. We will recruit a total of 100 participants and will randomly assign them to treatment and control arms based on a 50% probability of assignment. We also assume a 25% rate of dropout between baseline and the end of follow-up, resulting in an effective sample size of N=80. The dropout attrition rate is based on prior research on the SHUTi intervention where study dropout attrition at 1 year has been as high as 50%[50] although another study was as low as 4%[21] at the end of treatment evaluation. This may be due to the fact that differential dropout is frequently greater in active than control conditions in clinical trials due to the added psychological effort required in the active group and/or to attainment of treatment goals.

DISCUSSION

Knowledge gained from the SLEEP-I RCT will assist in improving the PDT which could then improve outcomes for individuals with chronic insomnia, which is one of the most common health concerns and imposes a significant burden on patients' lives.[1] Although CBT-I is the main treatment for insomnia, there are many challenges associated with in-person CBT-I such as poor access and lack of trained clinicians.[19] This will be the first controlled study to address these important gaps in clinical care by examining the impact of a mobile-delivered PDT device delivering CBT for insomnia using Hugo, a novel data science aggregating platform, to inform the field on the impact of a PDT for chronic insomnia on clinical domains (change in insomnia severity) and important related domains of patient satisfaction and healthcare utilisation.

Results from this study will advance our understanding of: (1) how novel ways of collecting and aggregating clinical and PROs data can support informed clinical decision-making; (2) digital therapeutic engagement and its relationship to clinical outcomes and (3) evaluation of data from linked devices by providing novel information on a prescription digital therapeutic for insomnia, connected with the Hugo platform. The outcome of this research will provide crucial data to inform the latest thinking about how data from both digital therapeutics and EHR systems can be used to evaluate real-world clinical and utilisation outcomes. These data will be used to demonstrate the value of implementing technology within healthcare systems, supporting the broad uptake of similar technology platforms. In addition, they will inform reimbursement discussions with payers to support coverage of and broad access to effective digital therapeutics.

This RCT has several potential study limitations. First, this study sample is quite small and will be relatively homogeneous given that participants will be recruited from sleep medicine clinics and may not represent those who only present at primary care or any medical disorders contraindicated with sleep restriction, and participants will be drawn from two urban sleep centres. Future studies should aim to enrol larger and more heterogeneous samples to improve the generalisability of the findings, such as those comparisons by sex and race/ethnicity to determine which patients most benefit from treatment, based on specific risk factors.[54–56] Second, this study relies on participants motivation and/or willingness to complete sleep diaries/intervention cores and PROs. Third, our findings will be based on self-report measures or PROs (eg, depression, stress, anxiety) versus a clinician-administered interview at all assessment points,

Ethics and dissemination

Ethics approval

The SLEEP-I RCT is sponsored by the National Evaluation System for health Technology Coordinating Center. Ethics approval was obtained independently at each of the two health systems, including at Yale University on 30 August 2021 (#2000029050) and Mayo Clinic on 14 February 2022 (#20–006319). Any amendments to the protocol are first reviewed by each of the two local institutional review boards prior to implementation and also receive approval from the study sponsor. This RCT is also

registered at ClinicalTrials.gov (NCT04909229) and was first posted on 1 June 2021.

Serious adverse events are not expected in this study where participants will be using their own digital devices. However, if there are device-related adverse events, they will be reported immediately, followed by a written report within five calendar days of the PIs becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigators will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project via email as they are reviewed by the PIs. The investigator team will make clear that any sync-able data, including PROs, will not be reviewed in real-time by researchers and will not be provided to the clinical care team and, therefore, any adverse or severe symptoms should be reported directly to their physician(s) or emergency room physicians as they would have in the normal course of care.

Dissemination plan

The results from this RCT will be presented at both scientific meetings and submitted for publication to peer-reviewed journals. Additionally, study results will be shared with stakeholders and enrolled study participants.

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Funding This work was supported by the Medical Device Innovation Consortium (MDIC) on behalf of the National Evaluation System for health Technology (NEST) Coordinating Center (6292-2019-R2TC-B18), initiative funded by the U.S. Food and Drug Administration (FDA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views nor the endorsements of the Department of Health and Human Services or the FDA. While MDIC provided feedback on project conception and design, the organisation will play no role in collection, management, analysis and interpretation of the data, nor preparation, review and approval of the manuscript. The research team, not the funder, made the decision to submit the manuscript for publication

Competing interests RPD reports research funding from the American Heart Association, the Canadian Institutes of Health Research and from the Medical Device Innovation Consortium (MDIC) as part of the National Evaluation System for health Technology Coordinating Center (NESTcc), Food and Drug Administration (FDA). JSR received research support through Yale University from Johnson and Johnson to develop methods of clinical trial data sharing, from the FDA to establish the Yale-Mayo Clinic Center for Excellence in Regulatory Science and Innovation (CERSI) program (U01FD005938), MDIC as part of the NESTcc, AHRQ (R01HS022882), NHLBI of the NIH (R01HS025164, R01HL144644), and from the Laura and John Arnold Foundation to establish the Good Pharma Scorecard at Bioethics International and to establish the Collaboration for Research Integrity and Transparency (CRIT) at Yale. NDS is currently employed by Delta Airlines; when he was employed by the Mayo Clinic, he reported receiving research support through Mayo Clinic from the Food and Drug Administration, the Centers of Medicare & Medicaid Innovation under the Transforming Clinical Practice Initiative, the Agency for Healthcare Research and Quality (grants R01HS025164, R01HS025402, R03HS025517 and K12HS026379), the National Heart, Lung and Blood Institute of the National Institutes of Health (grants R56HL130496, R01HL131535 and R01HL151662), the National Science Foundation, the Medical Device Innovation Consortium as part of the National Evaluation System for Health Technology, and the Patient-Centered Outcomes Research Institute to develop a Clinical Data Research Network. FT is an employee of Pear Therapeutics, that develops and distributes prescription digital therapeutics for health concerns and disease. Other authors report no other conflicts of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Institutional Review Board approval was obtained at Yale University (IRB number#2000029050) and the Mayo Clinic (IRB number#20-006319). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Upon completion of the clinical trial, data will be made available upon reasonable request.

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IRB Protocol# 2000029050

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY
YALE SCHOOL OF MEDICINE
YALE-NEW HAVEN HOSPITAL

Study Title: Randomized Controlled Trial Examining Real-World Effectiveness of a Prescription Digital Therapeutic for the Treatment of Insomnia

Principal Investigator (the person who is responsible for this research): Joseph Ross, MD, MHS

Phone Number: 203-785-2987
24-Hour Phone Number: 203-287-3550

Research Study Summary:

- We are asking you to join a research study.
- The purpose of this research study is to help us understand whether a digital Cognitive Behavioral Therapy intervention (CBT) for insomnia that is called PEAR-003b, created by Pear Therapeutics (https://peartherapeutics.com/) improves outcomes for patients with insomnia.
- Study procedures will include: Connecting your electronic health records with a patient-centered data sharing technology platform called Hugo, wearing a Fitbit, completing questionnaires at 5 different time points, and completing the digital CBT intervention (only if randomized to the intervention group).
- Only 1 visit is required.
- Your initial visit will take 2 hours maximum.
- There are some risks from participating in this study. Some questions in the questionnaires might make you feel uncomfortable. Additionally, wearing the Fitbit watch may also be uncomfortable for you, especially while you are sleeping.
- The study may have benefits to you. Knowledge gained from this study may improve outcomes for patients such as yourself who suffer from insomnia. Also, through the Hugo platform, you will have easy access to your medical records across all the institutions where you receive care. Wearing a Fitbit may also give you additional useful information regarding your health and fitness.
- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Why is this study being offered to me?

We are asking you to take part in a research study because you are between 22-64 years of age, have a diagnosis of chronic insomnia, and have presented to the Yale-New Haven Hospital

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(YNHH) Sleep Medicine Center. We are looking for 50 participants with insomnia to be part of this research study.

Who is paying for the study?

The Medical Device Innovation Consortium, through its National Evaluation System for health Technology Coordinating Center (NESTcc), which is funded by the U.S. Food and Drug Administration.

What is the study about?

The purpose of this research is for you to help us understand how we can improve outcomes for patients who have sleep problems (i.e. insomnia) by using a tailored, digital CBT intervention called PEAR-003b. Insomnia is one of the most common health concerns and imposes a significant burden on patients' lives. CBT is the main treatment for insomnia, but there are many challenges associated with in-person CBT such as lack of trained doctors, the cost and also poor access to this service. In light of this, PEAR-003b was developed. PEAR-003b is a digital CBT program that you can access on your mobile device or computer.

This study also uses a technology platform called Hugo Health that you can access on your mobile device or a computer that will gather together information (with your permission) from your online health records from your doctor's office, along with your responses to questionnaires from the researchers conducting this study and information about your activity/sleep from a Fitbit activity tracker that we will provide you.

What are you asking me to do and how long will it take?

If you agree to take part in this study, this is what will happen: we will obtain informed consent, collect contact information, and will randomize you into one of two groups: (1) Individuals who receive PEAR-003b (i.e. CBT-I) and Fitbit; or (2) Individuals who receive Fitbit only. By being in one of these two groups, particuarly the intervention group, this will allow us to determine upon study completion if the CBT-I improved outcomes for you or not. Both groups will be enrolled in Hugo.

Once we enroll you in the study we will ask you to complete questionnaires at 5 different time points (baseline, 9-week follow up; 21-week follow up, 35-week follow up; and 61-week follow up). These will include questions about insomnia severity, depression, stress, health-related quality of life, daytime sleepiness, and general anxiety. Both groups will receive materials on sleep hygiene and healthy sleep tips.

A description of study procedures is listed below in chronological order.

Setup process for Hugo data sharing platform and Fitbit (Both groups)

1. Using your own mobile device or computer, the study coordinator will help you to register for the Hugo platform. Registration for Hugo Health will require you to enter basic information including first name, last name, email address, and to choose a security password. You will then be prompted to accept standard terms and conditions and a privacy notice for the Hugo platform.
2. Using your personal mobile device (phone or tablet), you will check your email and click the confirmation link to activate your new Hugo account. If you do not have an email account and wish to create one, the study coordinator can help you set one up from a variety of free email providers.

3. Once your Hugo account is confirmed, the study coordinator will then walk you through the remaining steps to complete study enrollment in the Hugo platform.
4. The study coordinator will then show you how to access and complete your enrollment questionnaire. This questionnaire will be sent to you through email or text message, depending on which you would prefer, and will link to a multiple-choice survey in a web browser for you to complete. The study coordinator will help you with any technical questions you may have when you begin the survey.
5. The study coordinator will then help you set up an account with Fitbit, including connecting the Fitbit to both your phone and the Hugo platform.
6. The Hugo platform will prompt you to link your patient portal accounts by presenting a list of participating health systems. You can select the systems where you have received care and enter your patient portal credentials (all of these are password-protected). Should you forget your password, you can request a reset link be sent to your email account. The study coordinator can assist in setting up a new YNHH MyChart account, obtain your YNHH MyChart username, and help reset your YNHH MyChart password, if needed.
7. After your health records have been linked, the Hugo platform will display your health data, which can differ for the different health systems. The study coordinator will help you with the study information and be available to answer any questions related to data sharing.
8. The study coordinator will help you with setting up accounts for other health systems, if needed.
9. You will be asked to agree to share data from Hugo with the researchers. The medical record data being shared may include medications, problems, procedures, encounters, lab results, diagnoses, vital signs, and possibly other data that become available. From the Fitbit, the data being shared may include sleep patterns, movement (steps per-day), weight and BMI.
10. At the end of this consent form, we will ask you to give the researchers permission to see health information that you connect to the Hugo platform.

Please note: Researchers will not be watching or evaluating your responses to the questionnaires delivered via Hugo. None of the information collected in this study will be shared with your medical team. If at any point any medical issues arise, **please contact your doctor. In case of a life-threatening emergency, call 911 immediately.**

Setup process for PEAR-003b App (Intervention group only)

1. For those randomized to receive the PEAR-003b app, 14 days after enrollment the study coordinator will send you an email to your own mobile device with a registration access code as well as instructions on how to download the app from the Apple Store or Google Play.
2. You will then download and open the app using the registration access code. The app will then launch the onboarding sequence (approximately 8 introductory screens). After this is complete you can immediately begin Core 1 of the digital CBT-I treatment.
3. Core 2 will open 7 days after Core 1 is completed if you have completed at least 5 Sleep Diaries for the most recent 7 days. These will be Sleep Diaries you keep in the app. If 5 Sleep Diaries are not present, Core 2 will not open until they are complete.
4. All other Cores will open 7 days after the previous Core is completed. The study coordinator will help you with any technical questions you may have when you begin using the PEAR-003b app.

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Continuous Study Process
After the initial in-office set up is complete, you will be asked to perform the following tasks at home. If you have any questions or experience technical issues at any time, please reach out to the study coordinator's phone or email:

1. For all 63 weeks of this study, we ask that you wear your Fitbit as often as possible both during the day and while sleeping. We also ask that you turn on the Bluetooth feature on your phone at least once a week to allow your Fitbit to send data to your phone; if possible, it is preferred that you leave your Bluetooth on more often. If you are unfamiliar with the Bluetooth setting on your phone, the study coordinator will be able to help you.
2. Surveys will be sent to you throughout the duration of the follow-up period – at 9 weeks, 21 weeks, 35 weeks, and 61 weeks via a secure link sent through text or email from the Hugo platform.
3. For those in the intervention group we ask that you complete sleep diaries through the PEAR-03b app for the 9-week duration of the study. This will include information on what time you got in bed, how often you awoke during the night, and what time you got out of bed for the day.

Once the study is complete, we will remove your name and identifying information. At no point will we publish this information with individual data. Data from this study will be shared with investigators at Yale, the Mayo Clinic, and Pear Therapeutics to help us gain a better understanding about individuals with insomnia and what might lead to better outcomes. As a valued partner in this study, the information that you share will help us to learn more about the PEAR-03b CBT program and how it contributes to important patient and sleep outcomes – and whether Hugo and Fitbit can collect useful information which will inform future studies.

What are the risks and discomforts of participating?
While participating in this study, you will be asked to fill out multiple surveys, which will take some time and may be inconvenient. Some of the surveys may include sensitive questions that you may feel uncomfortable answering. If you feel uncomfortable answering any specific survey question, you will be able to skip these questions and continue with the rest of the survey. You may also find it inconvenient to wear the provided Fitbit device or connect it to your phone or tablet.

In following some intervention recommendations, participants may be asked to restrict sleep at certain times, which could lead them to initially feel more tired. This could potentially exacerbate the fatigue that many participants may already be experiencing.

How will I know about new risks or important information about the study?
If the study team learns that a participant has clinical depression during screening, or identifies a participant as having clinical depression during the study, the participant will be instructed to schedule an appoint with their primary care clinician; if the participant does not have a primary care clinician, the study team will offer to help the participant schedule an appointment with a primary care clinician at the New Haven Primary Care Consortium (NHPCC).

How can the study possibly benefit me?
Using the provided Fitbit, you may also gain additional awareness and information regarding your health and fitness. As a valued member of our research team, this research may benefit you directly in that knowledge gained from the results may improve outcomes for other patients

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with insomnia – through the use of the PEAR-003b mobile-delivered CBT application and Hugo platform, with linkage to Fitbit.

How can the study possibly benefit other people?
The benefit to science and other people may include a better understanding of how we can improve outcomes of people with insomnia.

Are there any costs to participation?
You will not have to pay for taking part in this study. The only costs include transportation and your time coming to the enrollment study visit, along with the time required to complete electronic surveys during the study. You are also responsible for data charges that may be incurred for utilizing online features of PEAR-003b, Hugo or Fitbit when not connected to Wi-Fi.

Will I be paid for participation?
You will be paid for taking part in this study. You will recieve $150 compensation in total for your participation via a Visa pre-paid card provided through the email address you used to create your Hugo account. This stipend will cover the consent process, initial set up and baseline questionnaire, questionnaires provided at 9 weeks, 21 weeks, 35 weeks, and 61 weeks along with the time it takes to sync and use the provided devices. You are responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments.

You will be paid $30 upon the completion of all questionnaires at each respective timepoint (i.e. Baseline, 9 weeks post-randomization, 21 weeks post-randomization, 35 weeks post-randomization, 61 weeks post-randomization), totaling $150.

What are my choices if I decide not to take part in this study?
Instead of participating in this study, you have some other choices.
You could:

- Get treatment without being in a study.
- Take part in another study.
- Not receive treatment for your disease.

How will you keep my data safe and private?
All identifiable information that is obtained in connection with this study will be treated as confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Once you enroll in the study you are given a specific study number. Your name will not appear directly on any of the questionnaires. Records of your participation in this study will be kept protected and treated as confidential. All Yale based study computers will be password-protected. All collected study data will be de-identified within 12 months of study completion. The data will be kept in this anonymous form indefinitely. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained. Representatives from the Yale Human Investigation Committee (the Committee that reviews, approves and monitors human subject research) may inspect study records during internal auditing procedures. However, they are required to keep all information confidential. When we publish the results of the research or talk about it in conferences, we will not use your name. If we want to use your name, we would ask you for your permission. We will also share

information about you with other researchers for future research but we will not use your name or other identifiers. We will not ask you for any additional permission.

What Information Will You Collect About Me in this Study?

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to a Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Demographics/socio-economic status (e.g., age, sex, ethnicity/race)
- Medical history
- Dates of admission to hospital and information about future hospital visits, procedures and medical care
- Emergency department encounters
- Medication data
- Outpatient visits
- Fitbit data (heart rate, tracking steps per day and/or exercise, sleep (total sleep time in minutes), and self-reported metrics such as weight, height and BMI)

HIPAA

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed below may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.
This authorization to use and disclose your health information collected during your participation in this study will never expire. However, you have the right to change your preference at any point in the future. Identifiers will be removed from the identifiable private information and after such removal, the information you contribute to this study could be used for future research or to help inform regulatory actions and can be distributed to another investigator for future research studies without additional informed consent from you or a legally authorized representative. Outside investigators will not know who you are. Private information such as your name, birth date or medical record number will not be shared with them.

☐ **By checking this box, I acknowledge my contribution to science and that my de-identified data collected as part of this study may be used in future research or for regulatory purposes without further consent from me.**

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How will you use and share my information?

We will use your information to conduct the study described in this consent form. We may share your information with:

- Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The Principal Investigators, research staff, and collaborators at both Yale University and the Mayo Clinic, who are assisting with this study
- Hugo Health, the company that owns the data sharing platform, in accordance with its Privacy Policy
- Pear Therapeutics (https://peartherapeutics.com/), the company that owns the PEAR-003b CBT application, in accordance with its Privacy Policy
- The US Food and Drug Administration (FDA), as regulators of medical devices
- Your sleep doctor, primary care physician and/or their staff

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential. Your information will not be used for commercial purposes.

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by contacting the study staff by telephone or e-mail.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered for this study after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to ensure the integrity of the study and/or study oversight. Once you withdraw, you will not receive further communication about this study. If you delete your Hugo account before your participation in this study ends, you will be automatically removed from the study.

What if I want to refuse or end participation before the study is over?

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

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We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

To withdraw from the study, you can call or e-mail a member of the research team at any time and tell them that you no longer want to take part.

What will happen with my data if I stop participating?
All data up to the date of withdrawl will be included in the study.

Who should I contact if I have questions?
Please feel free to ask about anything you don't understand. If you have questions later or if you have a research-related problem, you can email the PI (Joseph Ross at Joseph.Ross@yale.edu) or Research Associate (Alyssa Berkowitz at alyssa.berkowitz@yale.edu)

If you have questions about your rights as a research participant, or you have complaints about this research, you can call the Yale Institutional Review Boards at (203) 785-4688 or email hrpp@yale.edu.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

Participant Printed Name	Participant Signature	Date

Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date

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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: Randomized Controlled Trial Examining Real-World Effectiveness of a Prescription Digital Therapeutic for the Treatment of Insomnia and Depression

IRB#: 20-006319

Principal Investigator: Bhanu Kolla, M.D., and Colleagues

Key Study Information

This section provides a brief summary of the study. It is important for you to understand why the research is being done and what it will involve before you decide. **Please take the time to read the entire consent form carefully and talk to a member of the research team before making your decision.** You should not sign this form if you have any questions that have not been answered.	
It's Your Choice	This is a research study. Being in this research study is your choice; you do not have to participate. If you decide to join, you can still stop at any time. You should only participate if you want to do so. You will not lose any services, benefits or rights you would normally have if you choose not to take part.
Research Purpose	The purpose of this study is to help us better understand whether a digital Cognitive Behavioral Therapy (CBT) intervention for insomnia called Somryst (herein called PEAR-003b), created by Pear Therapeutics (https://peartherapeutics.com/), improves outcomes for patients with insomnia and depression. You have been invited to join this study because you are an adult with a diagnosis of chronic insomnia and depression, and you are visiting the Mayo Center for Sleep Medicine.
What's Involved	If you agree to participate, you will be asked to connect your electronic medical records from your Mayo Clinic Patient Online Services account, electronic medical records from any other health systems where you receive care, and information from a wearable device that we will provide to you, to a patient-centered health data

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	sharing platform called Hugo. Through Hugo, you will be asked to answer short questionnaires that will be sent to you via your choice of e-mail or text at five different time points. You will also be asked to complete the digital Cognitive Behavioral Therapy (CBT) intervention (only if randomized to the intervention group PEAR-003b). You do not need to have any technical skills to participate in this study; a member of the study team will help you set up your phone and connect your accounts.
Key Information	This study uses a technology platform called Hugo that you can access on your mobile phone or other device that is connected to the internet. Hugo collects data from multiple sources to create your own personal health record (PHR) and empowers you to share that data with researchers. You will have control over which data sources you connect to Hugo and will have the option to turn off data sharing at any time. Hugo has a one-way link to your health care clinicians: it can access information but cannot add any information to your health records. The Hugo platform, like many other personal health records, is not a covered entity; therefore, the HIPAA privacy rule does not apply to this platform. You will be required to sign a separate informed consent through Hugo. The Hugo platform does take all necessary precautions, including industry-standard encryption, to minimize privacy and security risks to personally identifiable information stored on behalf of study participants. Hugo makes publicly available its Security Statement (https://hugo.health/security), Privacy Notice (https://hugo.health/privacy-notice), and Terms of Service (https://hugo.health/terms-of-service/). While participating in this study, you will be asked to fill out multiple questionnaires, which will take some time and may be inconvenient. You may skip any questions that you feel uncomfortable answering. You may also find it inconvenient to wear the provided wearable device or connect it to your phone. We will provide you with a Fitbit for this study. The Fitbit will monitor your activity levels and sleep, and it will be yours to keep after the study is over. If you choose to participate, you can change your mind at any time and withdraw from the study.

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Learn More	If you are interested in learning more about this study, read the rest of this form carefully. The information in this form will help you decide if you want to participate in this research or not. A member of our research team will talk with you about taking part in this study before you sign this form. If you have questions at any time, please ask us.

Making Your Decision

Taking part in research is your decision. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision. Taking part in this study is completely voluntary and you do not have to participate.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you either a printed or electronic copy of this form to keep.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

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Contact Information

If you have questions about …	You can contact …
▪ Study tests and procedures ▪ Materials you receive ▪ Research-related appointments ▪ Research-related concern or complaint ▪ Research-related injuries or emergencies ▪ Withdrawing from the research study	**Principal Investigator(s):** Bhanu Kolla, M.D. **Phone:** 507-255-9230 **Study Team Contact:** Lindsay Emanuel **Phone:** (507) 422-6300 **Institution Name and Address:** Mayo Clinic 200 First Street SW Rochester, MN 55905
▪ Rights of a research participant	**Mayo Clinic Institutional Review Board (IRB)** **Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681
▪ Rights of a research participant ▪ Any research-related concern or complaint ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information ▪ Withdrawing from the research study	**Research Subject Advocate (RSA)** **(The RSA is independent of the Study Team)** **Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu
▪ Billing or insurance related to this research study	**Patient Account Services** **Toll-Free:** (844) 217-9591

Other Information:

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

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Why are you being asked to take part in this research study?

You have been invited to join this study because you are an adult with a diagnosis of chronic insomnia and depression, and you are visiting the Mayo Center for Sleep Medicine.

Why is this research study being done?

The purpose of this study is to help us better understand how we can improve outcomes for patients who have sleeping problems (i.e. insomnia) and daytime impairments (e.g. depression symptoms) by using a tailored, digital Cognitive Behavioral Therapy (CBT) intervention called PEAR-003b. Insomnia is one of the most common health concerns and imposes a significant burden on patients' lives. Adults suffering from insomnia also have a higher likelihood of depression, resulting in a reduced quality-of-life and higher rates of death and disability. Cognitive Behavioral Therapy (CBT) is the main treatment for insomnia, but there are many challenges associated with in-person CBT such as lack of trained doctors, the cost, and also poor access to this service. In light of this, PEAR-003b was developed. PEAR-003b is a digital Cognitive Behavioral Therapy (CBT) program that you can access on your mobile device or computer.

This study also uses a technology platform called Hugo Health that you can access on your mobile device or computer that will gather together information (with your permission) from your online health records from your doctor's office, your responses to questionnaires from the researchers conducting this study, and information about your activity/sleep form a Fitbit activity tracker that we will provide you.

Please note: The Hugo Health and PEAR applications used in this study are not affiliated with or monitored by Mayo Clinic.

Information you should know

Who is Funding the Study?

The Food and Drug Administration is funding the study. The Food and Drug Administration will pay the institution to cover costs related to running the study.

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Information Regarding Conflict of Interest:

Your healthcare provider may be referring you to this research study. If your healthcare provider is also an investigator on this study, there is the chance that his or her responsibilities for the study could influence his or her recommendation for your participation. If you prefer, your healthcare provider will be happy to refer you to another investigator on the research study team for you to decide if you want to participate in the study and to see you for the research study activities while you are in the study.

How long will you be in this research study?

You will be in this study for about 15 months.

What will happen to you while you are in this research study?

If you agree to take part in this study, this is what will happen: we will obtain informed consent, collect contact information, and will randomize you into one of two groups: (1) individuals who receive PEAR-003b (i.e. CBT-I) and Fitbit; or (2) individuals who receive Fitbit only. By being in one of these two groups, particularly the intervention group, this will allow us to determine upon study completion if the CBT-I improved outcomes for you or not.

Once we enroll you in the study, we will ask you to complete questionnaires at 5 different time points (baseline, 9-week follow up; 21-week follow up, 35-week follow up; and 61 week follow up). These will include questions about insomnia severity, depression, stress, health related quality of life, daytime sleepiness, and general anxiety. Both groups will receive materials on sleep hygiene and healthy sleep tips.
A description of study procedures is listed below in chronological order.

Setup process for Hugo data sharing platform and Fitbit (both groups)

1. Using your own mobile device or computer, the study coordinator will help you to register for the Hugo platform. Registration for Hugo Health will require you to enter basic information including first name, last name, email address, and to choose a security password. You will then be prompted to accept standard terms and conditions and a privacy notice for the Hugo platform.
2. Using your personal mobile device (phone or tablet), you will check your email and click the confirmation link to activate your new Hugo account. If you do not have an email

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account and wish to create one, the study coordinator can help you set one up from a variety of free email providers.

3. Once your Hugo account is confirmed, the study coordinator will then walk you through the remaining steps to complete study enrollment in the Hugo platform.
4. The study coordinator will then show you how to access and complete your enrollment questionnaire. This questionnaire will be sent to you through email or text message, depending on which you would prefer, and will link to a multiple-choice survey in a web browser for you to complete. The study coordinator will help you with any technical questions you may have when you begin the survey.
5. The study coordinator will then help you set up an account with Fitbit, including connecting the Fitbit to both your phone and the Hugo platform.
6. The Hugo platform will prompt you to link your patient portal accounts by presenting a list of participating health systems. You can select the systems where you have received care and enter your patient portal credentials (all of these are password-protected). Should you forget your password, you can request a reset link be sent to your email account. The study coordinator can assist in setting up a new Mayo Clinic patient portal account, obtain your Mayo Clinic patient portal username, and help reset your Mayo Clinic patient portal password, if needed.
7. After your health records have been linked, the Hugo platform will display your health data, which can differ for the different health systems. The study coordinator will help you with the study information and be available to answer any questions related to data sharing.
8. The study coordinator will help you with setting up accounts for other health systems, if needed.
9. You will be asked to agree to share data from Hugo with the researchers. The medical record data being shared may include medications, problems, procedures, encounters, lab results, diagnoses, vital signs, and possibly other data that becomes available. From the Fitbit, the data being shared may include sleep patterns, movement (steps per-day), weight and BMI.
10. At the end of this consent form, we will ask you to give the researchers permission to see health information that you connect to the Hugo platform.
11. On day 14 is when you will be randomized. You will be randomized 1:1 to the digital therapeutic or the control arm by the study coordinator using a randomization algorithm via Hugo. You will be notified if you are randomized to the treatment arm on day 14 by the study coordinator and will be provided with instruction on how to set up and create their Pear-003b account if randomized to the Pear-003b arm.

Please note: Researchers will not be watching or evaluating your responses to the questionnaires delivered via Hugo. None of the information collected in this study will be shared with your medical team. If at any point any medical issues arise, **please contact your doctor. In case of a life-threatening emergency, call 911 immediately.**

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**If you are unable to complete enrollment at this time, additional time can be scheduled within the next 3 days to complete the remaining steps.*

Setup process for PEAR-003b App (intervention group only)

1. For those randomized to receive the PEAR-003b app, 14 days after enrollment the study coordinator will send you an email to your own mobile device with a registration access code as well as instructions on how to download the app from the Apple Store or Google Play.
2. You will then download and open the app using the registration access code. The app will then launch in the onboarding sequence (approximately 8 introductory screens). After this is complete you can immediately begin Core 1 module of the digital CBT-I treatment.
3. Core 2 module will open 7 days after Core 1 module is completed if you have completed at least 5 Sleep Diaries for the most recent 7 days. These will be Sleep Diaries you keep in the app. If 5 Sleep Diaries are not present, Core 2 module will not open until they are complete.
4. All other Cores (modules) will open 7 days after the previous Core (module) is completed. The study coordinator will help you with any technical questions you may have when you begin using the PEAR-003b app.

   Each module (Core) includes weekly Insomnia Severity Index assessment, sleep diaries, and a learning focus. The PHQ8 is also included at the beginning of Cores 1, 3, and 5. There is a Self Assessment of patient sleep problems and Goal Setting selection in Core 1. Core 6 includes a final Self Assessment and Goals assessment to review progress made in the treatment. Each module is a combination of written material, expert explanation videos, interactions, and vignettes (written and video) of "typical" users and their journeys. Each module (Core) focuses on a different aspect of sleep behaviors and strategies

Continuous Study Process

After the initial in-office set up is complete, you will be asked to perform the following tasks at home. If you have any questions or experience technical issues at any time, please reach out to the PI or study coordinator's phone or email:

- For all 63 weeks of this study, we ask that you wear your Fitbit as often as possible both during the day and while sleeping. We also ask that you turn on the Bluetooth feature on your phone at least once a week to allow your Fitbit to send data to your phone; if possible, it is preferred that you leave your Bluetooth on more often. If you are unfamiliar with the Bluetooth setting on your phone, the study coordinator will be able to help you.
- Surveys will be sent to you throughout the duration of the follow-up period – at 9 weeks, 21 weeks, 35 weeks, and 61 weeks via a secure link sent through text or email from the Hugo platform.

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- The study coordinator will contact you at weeks 35 and 61 to ask about care at other health systems and the Hugo platform will be checked to ensure that data from those health systems are included. You will be asked to link those health systems or provide data, as appropriate.
- For those in the intervention group (PEAR-003b) we ask that you complete sleep diaries through the PEAR-03b app for the 9-week duration of the study. This will include information on what time you got in bed, how often you awoke during the night, and what time you got out of bed for the day.

Once the study is complete, we will remove your name and identifying information. At no point will we publish this information with individual data. Data from this study will be shared with investigators at Yale, the Mayo Clinic, and Pear Therapeutics to help us gain a better understanding about individuals with insomnia and depression and what might lead to better outcomes. As a valued partner in this study, the information that you share will help us to learn more about the PEAR-03b CBT program and how it contributes to important patient and sleep outcomes – and whether Hugo and Fitbit can collect useful information which will inform future studies.

What are the possible risks or discomforts from being in this research study?

As with all research, there is a chance that confidentiality could be compromised; however, we take precautions to minimize this risk.

The risk to your privacy is that the Hugo platform collects personally identifiable information (like your name and where you go to the doctor) and protected health information (like the conditions you have and medications you take). The Hugo platform is not considered a "covered entity" under the Health Insurance Portability and Accountability Act of 1996 (HIPAA); this means that the HIPAA privacy rule does not apply to this platform. The Hugo platform does take all necessary precautions, including industry-standard encryption, to minimize privacy and security risks to your stored personally identifiable information. To learn more about Hugo's commitment to the security and privacy of your data, you can visit the following links: Security Statement (https://hugo.health/security), Privacy Notice (https://hugo.health/privacy-notice), Terms of Service (https://hugo.health/terms-of-service/).

While participating in this study, you will be asked to fill out multiple surveys, which will take some time and may be inconvenient. Some of the surveys may include questions that you feel uncomfortable answering. If you feel uncomfortable answering any specific survey question, you will be able to skip these questions and continue with the rest of the survey. You may also find it inconvenient to wear the provided Fitbit device or connect it to your phone.

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In following some intervention recommendations, participants may be asked to restrict sleep at certain times, which could lead them to initially feel more tired. This could potentially exacerbate the fatigue that many participants may already be experiencing.

Are there reasons you might leave this research study early?

You may decide to stop at any time.

In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time if it is in your best interest, if you don't follow the study procedures, or if the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

What if you are injured from your participation in this research study?

Where to get help:

If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries:

Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. Treatment costs for research-related injuries not covered by your insurance will be paid by Mayo Clinic.

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What are the possible benefits from being in this research study?

A possible benefit of this study is that you will have easy access to the information contained in your Mayo Clinic and outside health records that you connect to Hugo Health. Using the provided Fitbit, you may also gain additional awareness and information regarding your health and fitness. The knowledge gained from the results may improve outcomes for other patients with insomnia and depression through the use of the PEAR-003b mobile-delivered CBT application and Hugo platform with linkage to Fitbit.

What alternative do you have if you choose not to participate in this research study?

If you decide not to participate in this study, you will still have access to medical care and to your medical records as you would normally. You may decline to participate in the study for any reason without affecting your medical care.

What tests or procedures will you need to pay for if you take part in this research study?

The platform, technology, devices and applications used in this study will be provided to participants free of cost. Updates to the platform will also be provided free of cost for the duration of the study.

Participants will still be responsible for any costs associated with transportation to come to the enrollment study visit and routine follow up or health care visits that occur in the context of standard care. Participants will still be responsible for any co-payments required by their insurance company for standard treatments as well.

Participants are responsible for data charges that may be incurred from using online features of the Hugo or smart watch mobile applications when not connected to Wi-Fi.

If you have billing or insurance questions call Patient Account Services at the telephone number provided in the Contact Information section of this form.

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Will you be paid for taking part in this research study?

You will be paid for taking part in this study. You will receive. $150 compensation in total for your participation via a Visa pre-paid card provided through the email address you used to create your Hugo account. This stipend will cover the consent process, initial set up and baseline questionnaire, questionnaires provided at 9 weeks, 21 weeks, 35 weeks, and 61 weeks along with the time it takes to sync and use the provided devices. You are responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments.

You will be paid $30 upon the completion of all questionnaires at each respective timepoint (i.e. Baseline, 9 weeks post-randomization, 21 weeks post-randomization, 35 weeks post-randomization, 61 weeks post-randomization).

Will your information or samples be used for future research?

Identifiable information such as your name, Mayo Clinic number, or date of birth may be removed from your information or samples collected in this study, allowing the information or samples to be used for future research or shared with other researchers without your additional informed consent.

Identifiable data through the Hugo dashboard will be viewable by our collaborators from Yale New Haven for monitoring and compliance reasons.

How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and

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why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission (or "authorization") to Mayo Clinic.

Your health information may be collected from:

- Past, present and future medical records at Mayo Clinic and all health systems that you import into Hugo.
- Data collected from the provided Fitbit during the 63-week follow-up period.
- The Hugo platform (including pharmacy records and imported claims using CMS Blue Button).
- Research procedures, such as phone calls, e-mails, and research questionnaires as part of this research.

Your health information will be used and/or given to others to:

- Do the research.
- Report the results.
- See if the research was conducted following the approved study plan, and applicable rules and regulations.

Your health information may be used and shared with:

- Mayo Clinic research staff involved in this study.
- Researchers involved in this study at other institutions (Yale-New Haven Hospital, Pear Therapeutics, and Hugo Health).
- The sponsor(s) of this study and the people or groups hired by the sponsor(s) to help perform this research.
- The Mayo Clinic Institutional Review Board that oversees the research.
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- A group that oversees the data (study information) and safety of this research.

The data collected in your Hugo account, including data from any portals you connect and responses to any questionnaires you complete, will not be transferred back to your medical record. This means that your doctors will not see your responses to the study questionnaires or the information from your wearable device.

All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at Mayo Clinic is required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and, therefore, may not be

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required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential. In addition, even though Hugo Health is not required to comply with HIPAA, they maintain the highest standards of confidentiality and security of your information and will never share your data beyond this study without your expressed explicit permission as described in their privacy notice provided when you sign up for Hugo.

How your information may be shared with others:

While taking part in this study, you will be assigned a code that is unique to you, but does not include information that directly identifies you. This code will be used if your study information is sent outside of Mayo Clinic. The groups or individuals who receive your coded information will use it only for the purposes described in this consent form.

If the results of this study are made public (for example, through scientific meetings, reports or media), information that identifies you will not be used.

In addition, individuals involved in study oversight and not employed by Mayo Clinic may be allowed to review your health information included in past, present, and future medical and/or research records. This review may be done on-site at Mayo Clinic or remotely (from an off-site location). These records contain information that directly identifies you. However, the individuals will not be allowed to record, print, or copy (using paper, digital, photographic or other methods), or remove your identifying information from Mayo Clinic.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Rights and Permissions

Participation in this study is completely voluntary. You have the right not to participate at all. Even if you decide to be part of the study now, you may change your mind and stop at any time. You do not have to sign this form, but if you do not, you cannot take part in this research study.

Deciding not to participate or choosing to leave the study will not result in any penalty. Saying 'no' will not harm your relationship with your own doctors or with Mayo Clinic.

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If you cancel your permission for Mayo Clinic to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

You can cancel your permission for Mayo Clinic to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
201 Building 4-60
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing: emanuel.lindsay@mayo.edu.

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission for Mayo Clinic to use and share your health information lasts forever, unless you cancel it.

There is no expiration or end date related to the Sponsor's use of your health information received from Mayo Clinic as part of this study.

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Enrollment and Permission Signatures

Your signature documents your permission to take part in this research.

	/ /	: AM/PM
Printed Name	Date	Time

_____
Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

	/ /	: AM/PM
Printed Name	Date	Time

_____
Signature