CBT-I AND LIGHT THERAPY

Protocol

Feasibility of Cognitive Behavioral Therapy vs. Bright Light Therapy
to Treat Insomnia and Fatigue: an RCT

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Funding Sponsor	Bayer Corporation
Original Protocol Date:	1 November 2021

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Protocol Synopsis

Title	Feasibility of Cognitive Behavioral Therapy Vs. Bright Light Therapy to Treat Insomnia and Fatigue: an RCT
Short Title	CBT-I and Light Therapy
Methodology	In a single site, 3-arm (Cognitive Behavioral Therapy [CBT-I] group; Bright Light Therapy group; Standard of Care group), parallel, randomized controlled trial we will enroll 36 subjects (n=12 per group) to assess the feasibility of Bright Light Therapy compared to CBT-I in subjects with pulmonary arterial hypertension (PAH) to treat insomnia (difficulty initiating sleep or maintaining sleep) and fatigue.
Study Duration	10 Weeks
Study Center(s)	University of Pennsylvania
Objectives	Primary: • To assess the recruitment and retention rates of CBT-I and Bright Light Therapy. Secondary: • To compare the effects of CBT-I and Bright Light Therapy to Standard of Care on (insomnia and fatigue severity) and secondary (wake after sleep onset and sleep onset latency) outcomes. • To test the effects of CBT-I and Bright Light Therapy to Standard of Care on the secondary outcome physical activity. • To test the effects of CBT-I and Bright Light Therapy to Standard of Care on the secondary outcomes: depression, dyspnea and QOL.
Number of Subjects	Approximately 36 subjects expected to be enrolled from Penn, 12 subjects in each arm.

Main Inclusion and Exclusion Criteria	**Inclusion Criteria** 1. Signed informed consent prior to initiation of any study mandated procedure. 2. Male and female subjects ≥ 18 years of age 3. Diagnosis of PAH, including: a. Idiopathic (IPAH) b. Heritable (HPAH) c. Drugs and toxin induced PAH d. PAH associated with: i. Connective tissue disease; ii. Human immunodeficiency virus (HIV) infection; iii. Congenital heart disease; or iv. Portal hypertension 4. Documented hemodynamic diagnosis of PAH by right heart catheterization (RHC), prior to enrollment showing: a. mPAP ≥ 25 mmHg; and b. PAWP or LVEDP ≤ 15 mmHg. 5. On targeted stable medication doses for 3 months prior to enrollment 6. Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance 8a > 8 (raw score); > 30 (t score) at enrollment 7. Fatigue Severity Scale (FSS) > 35 at enrollment **Exclusion Criteria** 1. Enrolled in another clinical trial 2. Untreated obstructive sleep apnea, 3. Subjects with left-sided valvular disease (more than moderate mitral valve stenosis or insufficiency or aortic stenosis or insufficiency), pulmonary artery or valve stenosis, or ejection fraction < 45% on echocardiography before enrollment 4. Hospitalized or acutely ill 5. Any eye disease such as, but not limited to, cataracts, glaucoma, retinal disorders (e.g. macular degeneration), or previous eye surgery. 6. Subjects with photosensitivity (e.g. epilepsy) 7. Manic-depressive psychosis or Bipolar Disorder
Data Analysis	We will use intention-to-treat analyses. First, we will calculate the frequencies and percentages for all demographic (e.g. sex) and clinical (e.g. medications) categorical variables and use Fisher's exact test to compare baseline differences between groups. We will obtain means, medians, standard deviations, and interquartile-ranges for all continuous demographic (e.g. age) and clinical variables (e.g. body mass index) and use t-tests to compare baseline differences between groups. We will use non-parametric tests to compare the groups if the data do not follow normal distribution. To maintain experiment-wise type I error rate at the nominal level ($\alpha = 0.05$), we will conduct an omnibus test for overall differences between the three groups using the ANOVA approach. In the presence of a significant overall difference, we will conduct post hoc comparison of the two treatment conditions with the Standard of Care group using the Dunnett approach. We will verify the assumptions related to the ANOVA using residuals. We will use the non-parametric Kruskal-Wallis approach if the data do not satisfy the normal distribution assumption. If our preliminary analysis identifies group differences at baseline, we will adjust for the difference at baseline and perform analysis of covariance. Analyses will be primarily conducted using the R statistical environment.
Data and Safety Monitoring Plan	Connie Ulrich PhD, RN, FAAN will monitor the study.

Background and Study Rationale

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations.

1. Introduction

Pulmonary arterial hypertension (PAH) is a chronic, debilitating disease that leads to right heart failure and death. Subjects with PAH can have severe symptoms such as fatigue and sleep disturbance.[1] Subjects with PAH have profound limitations in physical functioning resulting in premature disability and impaired quality of life (QOL).[7] Symptoms in PAH are burdensome.[11] Medication regimens in PAH can also be complex. To date, there are no non-pharmacological interventions that have been tested in PAH to treat insomnia and symptoms such as fatigue.

2. Background

2.1.1 Definition and characterization of PAH

Pulmonary arterial hypertension (PAH) is a pulmonary vasculopathy that leads to dyspnea, exercise limitation, right heart failure and death if left untreated. PAH is defined by mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg with a normal pulmonary capillary wedge pressure in the absence of other causes of pulmonary hypertension, such as heart or parenchymal lung disease, sleep apnea, thromboembolic disease, or other systemic disease.

2.1.2 Insomnia

Insomnia is the most common sleep disturbance. Insomnia is defined as trouble initiating or maintaining sleep which is associated with daytime consequences such as fatigue and daytime sleepiness that is not due to environmental circumstances or a lack or opportunity to sleep.[12] Sleep disturbance is prevalent in PAH (66%).[13] In a study of subjects with PAH we found 21% had mild sleep disturbance; 22% moderate sleep disturbance and 16% severe sleep disturbance.[1] Our preliminary actigraphy data show that the majority of subjects with PAH (92%, N=60) have difficulty maintaining sleep (wake after sleep onset-median 69.3 minutes IQR (52.9-93.1).[3] Increased daytime sleepiness is associated with worse PAH symptoms and QOL.[3] In PAH, increasing levels of sleep disturbance are associated with worse symptoms (e.g. dyspnea), psychological distress, decreased QOL and physical ability.[1] Insomnia (48%) and poor sleep quality (73%) in pulmonary hypertension (PH) are common and associated with depression, dyspnea and diminished QOL.[2] Sleep quality was compared between subjects with idiopathic PAH (IPAH) and healthy controls.[14] Those with IPAH had significantly worse sleep quality ($p<0.01$) and worse functional capacity (6 minute walk distance (6MWD)). Over half (57%) of subjects with PAH report that difficulty sleeping interferes with their lives.[11]

2.1.3 Fatigue

Fatigue is defined as an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's ability to carry out daily activities and function.[15] We found over 90% of subjects with PAH report fatigue that interferes with their life.[16] In addition, more than 40% of PAH subjects are disabled, with fatigue as a strong risk factor for disability.[16] Fatigue is associated with dyspnea, physical disability and psychological distress in PAH. A recent study of 120 subjects with PH found a high prevalence of "severe" to "very severe" fatigue.[17] Those taking phosphodiesterase inhibitors plus endothelin receptor antagonists combinations reported less fatigue.

2.1.4 Physical Activity

Physical Activity is decreased in PAH. In a study of subjects with PAH those who had poor sleep quality also had shorter 6MWD (IPAH 338 ± 23 vs. 441 ± 29 meters, $p < 0.05$).[18] Using actigraphy, we found

subjects with PAH are more sedentary compared to healthy individuals ($p<0.001$). In a sample of women with PAH we found that most of their time was spent sedentary (85%) and only 10% of their time was engaged in low levels of activity.[19] The 6MWD was positively associated with physical activity bouts ($r=0.64$, $p=0.011$) and worse energy levels were associated with lower average activity levels (estimate= -13.965, $p=0.013$).[19] Average physical activity (counts per minute) for the subjects ranged between 172.9 + 71.0 and 175.7 + 63.3 over 2 weeks of actigraphy, similar to those seen in another study of actigraphy in PAH.[20] Normative data from the National Health and Nutritional Examination Survey (NHANES) showed average activity counts per minute for females age 60-69 were 251 and 170 for those 70 years and older. Our PAH sample was younger (mean age 52 years), but had much lower activity counts, suggesting that women with PAH have very limited activity levels even compared to individuals from the general population more than 2 decades older. Improving insomnia and fatigue levels may have a positive impact on physical activity in PAH.

2.1.5 Bright Light Therapy

Light is an important factor in regulating sleep and wakefulness. Light input is received by photoreceptors in the eye, which is communicated via the retinohypothalamic tract to the suprachiasmatic nucleus, where it regulates circadian rhythms. Light also inhibits the secretion of melatonin, a hormone that regulates the sleep-wake cycle. Therefore, Bright Light Therapy has been used as a treatment for sleep disorders including insomnia and circadian rhythm disorders. Bright Light Therapy is a simple, safe and low cost treatment, with only mild side effects reported such as headache.[21]

In a meta-analysis of the effects of light therapy on sleep problems, the effect sizes for fatigue (Hedge's $g=0.47$) were larger than for sleep variables (sleep onset latency Hedge's $g=0.42$; wake after sleep onset Hedge's $g=0.35$).[8] Bright Light Therapy was used to treat cancer-related fatigue. Patients (N=81) were randomized to 30 minutes of either Bright Light Therapy or dim light daily for 28 days.[9] In another study of cancer survivors with cancer-related fatigue (N=44) patients were randomized to either Bright Light Therapy or dim light for 30 minutes in the morning for 4 weeks. Sleep efficiency (percentage of time spent asleep while in bed) improved in the Bright Light Therapy group ($p=0.003$) with a large effect size (partial $\eta 2 = 0.28$).[22]

2.1.6 Cognitive Behavioral Therapy for Insomnia (CBT-I)

CBT-I is a multi-component intervention that includes behavioral and cognitive strategies. The cognitive portion of therapy helps subjects recognize and change beliefs that are affecting their ability to sleep. The behavioral component helps the subject develop good sleep habits and may include: relaxation therapy, stimulus control, sleep restriction, sleep hygiene.[1]

A literature review was conducted to determine the effects of insomnia in other medical and psychiatric conditions (e.g. chronic pain, HIV, depression, posttraumatic stress disorder, generalized anxiety).[2] Effect sizes (Cohen's d) ranged from 0.35-2.2. Not only did the review indicate that CBT-I improved insomnia, but CBT-I may also indirectly improve other medical and psychological endpoints. For example, in a study including cancer subjects with insomnia stimulus control, relaxation techniques, sleep hygiene, and cognitive approaches were used to decrease worry and emotional arousal prior to initiating sleep. There were significant improvements in sleep quality, sleep latency, time awake after sleep onset, sleep efficiency, number of nightly awakenings, and total sleep time (all $p<0.05$). Additionally, subjects reported a reduction in fatigue ($p=0.022$) and improvement in functioning ($p=0.015$).

The evidence supports the use of CBT-I for the treatment of insomnia, but CBT-I is not as effective with combating waking symptoms of fatigue. While we have some evidence that Bright Light Therapy works to improve sleep and fatigue the evidence is inconclusive. The evidence thus far highlights the need for research to test the efficacy of CBT-I and Bright Light Therapy in disease specific conditions and symptoms such as insomnia and fatigue.

3. Study Objectives

A single site, 3-arm (CBT-I group; Bright Light Therapy group; Standard of Care group), parallel, randomized controlled trial in subjects with insomnia, fatigue and PAH will be conducted.

3.1 Primary Objective

- To assess the feasibility (recruitment and retention rates) of CBT-I and Bright Light Therapy in patients with PAH.

3.2 Secondary Objectives

- To compare the effects of CBT-I and Bright Light Therapy to Standard of Care on insomnia and fatigue severity and wake after sleep onset and sleep onset latency outcomes.
- To test the effects of CBT-I and Bright Light Therapy to Standard of Care on physical activity.
- To test the effects of CBT-I and Bright Light Therapy to Standard of Care on: depression, dyspnea and QOL.

4. Study Population and Duration of Participation

4.1 Duration of Study Participation

Each subject will be in the study for approximately 10 weeks.

4.2 Total Number of Subjects

Recruitment will end when 36 subjects are enrolled. These subjects will be screened and enrolled from Penn only.

4.3 Inclusion Criteria

- Signed informed consent prior to initiation of any study mandated procedure.
- Male and female subjects ≥ 18 years of age
- Diagnosis of PAH belonging to one of the following subgroups of Group 1 PH according to the updated clinical classifications:
    - Idiopathic (IPAH)
    - Heritable (HPAH)
    - Drugs or toxins induced PAH
    - PAH associated with one of the following:
        - Connective tissue disease;
        - Human immunodeficiency virus (HIV) infection;
        - Congenital heart disease; or
        - Portopulmonary hypertension
- Documented hemodynamic diagnosis of PAH by right heart catheterization (RHC), prior to enrollment showing:
    - mPAP > 25 mmHg; and
    - PAWP or LVEDP ≤ 15 mmHg.
- On targeted stable therapy for 3 months prior to enrollment
- Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance 8a > 8 (raw score) at enrollment
- Fatigue Severity Scale (FSS) > 35 at enrollment

4.4 Exclusion Criteria

- Pregnant
- Enrolled in another clinical trial
- Untreated obstructive sleep apnea
- Subjects with left-sided valvular disease (more than moderate mitral valve stenosis or insufficiency or aortic stenosis or insufficiency), pulmonary artery or valve stenosis, or ejection fraction < 45% on echocardiography before enrollment
- Hospitalized or acutely ill
- Any eye disease such as, but not limited to, cataracts, glaucoma, retinal disorders (e.g. macular degeneration), or previous eye surgery
- Subjects with photosensitivity (e.g. epilepsy)
- Manic-depressive psychosis or Bipolar Disorder

4.5 Subject Recruitment

In this RCT we will recruit 36 subjects with insomnia, fatigue and PAH from the University of Pennsylvania PVD Center who meet the inclusion criteria, to address our study aims. Patients with PAH will be screened for insomnia (PROMIS Sleep Distance > 8-raw score), fatigue (Fatigue Severity Scale >35). We estimate that a minimum of 50% of our subject pool (approximately 250) will meet eligibility criteria (insomnia and fatigue) based on our preliminary data. Therefore, anticipating a conservative recruitment rate, we have planned for recruitment of 36 subjects over the course of 9 months.

4.6 Populations Vulnerable to Undue Influence or Coercion

Subjects will be informed that participation is voluntary and that they can change their mind at any time. They will be informed that participation in this research study is by choice, and if they choose to participate or not participate their clinical care will not be affected. Research coordinators will be mainly responsible for approaching the potential subjects. The rights and welfare of Penn employees and students that could potentially enroll in this study will be protected because the identity of the participants in the study will remain anonymous to everyone at Penn except those on the study staff. Study records will be kept in locked file cabinets and electronic data will be accessible by password only. The decision of the subject to enroll or withdraw from the study will have no effect on their standing at Penn. Finally, eligible patients need to have a diagnosis of pulmonary hypertension, making it a very minute population that could potentially be eligible.

5. Randomization

A Permuted Block Randomization scheme using SAS, consisting of random blocks of 3 and 6 will be used for randomization of subjects. Opaque, sealed consecutively numbered envelopes will be assembled that either have a “CBT-I”; “Bright Light Therapy” or “Standard of Care” card within the study packet. All study packets will look the same and be the same thickness and weight. After informed consent is obtained and screening measures are completed, the research coordinator will select the next consecutive envelope of study materials to reveal the arm of the study each subject will be assigned. Study personnel analyzing the data will be blinded to the treatment arm those analyzing the actigraphs will also be blinded.

6. Study Assessments

6.1 Informed Consent

A member of the Research Team will review the purpose and procedures of the study, including completing either Cognitive Behavioral Therapy sessions or wearing Re-timer device for Bright Light Therapy, physical activity monitoring and questionnaires. The Research Coordinator will discuss the risks and benefits of participating, compensation for their time, who will be enrolled, the target number of subjects to be enrolled, how subject privacy and confidentiality will be protected, as well as the fact that subjects can drop out at any time. Subjects will be given an opportunity to ask questions about the study and will be encouraged to speak to their family, friends, and PH doctor about study participation. Subjects will be given the opportunity to consent, to participate or decline. If the consent process is taking place in clinic (in person), the subject will sign the consent form and be handed a copy for their records. If the consent process is taking place over the phone or via a web-meeting software, the subject will receive an email with a link to the REDcap electronic informed consent form. The subject will electronically sign the electronic consent form and have the opportunity to save and print a copy for their own records.

6.2 Demographics and Medical History Review

Demographic information (sex, age, race, and ethnicity) and a complete medical history will be obtained from each subject. A complete subject history of PAH, including diagnosis, associated illness and diseases will be collected by chart review and subject interview.

6.3 Medication Review

A list of current medications will be documented for each subject. Medications (especially changes in medication) will be updated at each scheduled visit and/or telephone call. A detailed history of PAH specific medications will also be documented.

6.4 Questionnaires

6.4.1 Fatigue Severity Scale (FSS)

The FSS is a 9-item self-report questionnaire that measures how fatigue affects motivation, exercise, physical functioning, carrying out duties, and interference with work, family or social life. The items are measured on a 7-point Likert scale (e.g. 1=strongly disagree; 7=strongly agree). Scoring is completed by summing the scores. Score range from 9-63; higher scores indicate increased fatigue. Scores greater than 35 are considered abnormal and/or increased fatigue. Subjects will complete the questionnaire at screening, on Day 1 and on Week 9.

6.4.2 PROMIS® Sleep Disturbance

The adult 8-item PROMIS Sleep Disturbance 8a questionnaire was used to measure self-reported perceptions of sleep quality, depth, and restoration within the past seven days. This includes perceived difficulties falling asleep and staying asleep, as well as sleep satisfaction. The measure uses a 5-point Likert scale, and the raw score was converted to a standardized *T*-score using conversion tables published on the PROMIS website (nihpromis.org), with higher scores indicating greater sleep/wake disturbances.
Each item on the measure is rated on a 5-point scale (1=never; 2=rarely; 3=sometimes; 4=often; and 5=always) with a range in score from 8 to 40 with higher scores indicating greater severity of sleep disturbance. A single Physical Function capability score is obtained from a short form. The T-scores are interpreted as follows: < 55 none to slight; 55.0-59.9 mild; 60.0-69.9 moderate; >70 severe. Raw scores range from 8-40. Subjects will complete at screening, on Day 1 and on Week 9.

6.4.3 Insomnia Severity Index (ISI)

The ISI is a 7-item self-report questionnaire assessing the severity and impact of insomnia. The ISI evaluates, severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, and distress caused by the sleep

difficulties. A 5-point Likert scale is used to rate each item on a 0-4 scale (0 = no problem; 4 = very severe problem). Total scores range 0-28 (0-7 = no insomnia; 8-14 = sub-threshold insomnia; 15-21 = moderate insomnia; and 22-28 = severe insomnia). Subjects will complete the questionnaire on Day 1 and on Week 9.

6.4.4 EmPHasis-10

The emPHasis-10 is a pulmonary hypertension-specific questionnaire which is scored from 0-50 (with higher scores indicating worse QOL). Subjects will complete the questionnaire on Day 1 and on Week 9.

6.4.5 PROMIS® Physical Function Questionnaire

This is an 8-itme questionnaire that measures self-reported capability rather than actual performance of physical activities. This includes the functioning of one's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands. Each item on the measure is rated on a 5-point scale (1=never; 2=rarely; 3=sometimes; 4=often; and 5=always) with a range in score from 8 to 40 with higher scores indicating greater severity of sleep disturbance. A single Physical Function capability score is obtained from a short form. The T-scores are interpreted as follows: < 55 none to slight; 55.0-59.9 mild; 60.0-69.9 moderate; >70 severe. Subjects will complete at screening, on Day 1 and on Week 9.

6.4.6 Center for Epidemiological Studies- (CES-D)

The Center for Epidemiological Studies-Depression (CES-D) is a 20-item measure that asks how often over the past week they experienced symptoms associated with depression, such as restless sleep, poor appetite, and feeling lonely. Response options range from 0 to 3 for each item (0 = Rarely or None of the Time, 1 = Some or Little of the Time, 2 = Moderately or Much of the time, 3 = Most or Almost All the Time). Scores range from 0 to 60, with high scores indicating greater depressive symptoms. A score of 16 points or more is considered depressed. Subjects will complete the questionnaire on Day 1 and on Week 9.

6.4.7 Pittsburgh Sleep Quality Index (PSQI)

The PSQI measures sleep disturbance and quality. There are seven domains: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications and daytime dysfunction on most nights over the past month. The PSQI is self-administered and contains 19 sleep-related questions. Questions are rated on a 0-3 scale. The global score is calculated from the seven components. Scores range form 0-21; higher scores indicated worse sleep quality. Scores greater than 5 indicate worse sleep disturbance and poor sleep quality. The sensitivity of the PSQI is 89.6% and 86.5% specificity to distinguish good and poor sleepers. Subjects will complete the questionnaire on Day 1 and on Week 9.

6.4.8 PROMIS Short Form (SF) v 1.0- Dyspnea-Severity 10a

The PROMIS Dyspnea measures self-reported severity. This is self-administered and measures dyspnea severity during activity. The measure contains 10 items on a Likert scale. Each activity is rated in terms of degree of dyspnea (no shortness of breath, mildly short of breath, moderately short of breath, severely short of breath) while engaging in the activity over the past 7 days, with higher scores reflecting greater levels of dyspnea. Respondents who indicate that they did not perform an activity in the past 7 days will not produce a score for that item. Subjects will complete the questionnaire on Day 1 and on Week 9.

Urine pregnancy Test:

Female subjects who are not post-menopausal will be sent a urine pregnancy test with instructions. They will take a picture of the results and will send to the Research Coordinator to confirm the subject is not pregnant.

6.5 Actigraphy

Physical activity will be measured by actigraphy. An actigraph is a highly sensitive motion sensor that records movement and provides objective data regarding daytime activity and duration of sleep. Actigraphs are small, non-invasive devices worn on the wrist and do not interfere with usual daily activities or function. Actigraphy is a valid and reliable measure of sleep-wake patterns and physical activity by continuously recording activity over a specified time period (e.g., 1 minute intervals). Subjects will be mailed an actigraph and begin wearing the wrist actigraph on Day 1 and will wear the wrist actigraph for 7 days. Subjects will return the actigraph with a self-addressed pre-paid envelope. At the beginning of Week 9, subjects will be mailed an actigraph to be worn for 7 days during the last week of the intervention. Subjects will return the actigraph with a self-addressed pre-paid envelope. Actigraphy will be analyzed in counts per minute by computer software.

6.6 Sleep and Activity Diary

The Sleep Diary form is a self-reported questionnaire to collect data about the patient's sleep/wake patterns. Subjects will complete a sleep and activity diary (e.g. time to bed, time out of bed, exercise), each day of the study, starting on Day 1 for the CBT-I group. Those conducting the CBT-I sessions will review with subjects at the weekly sessions. The Bright Light Therapy group and Standard of Care group will begin on Day 1 for 7 days for Week 1 and for 7 days in Week 9 via REDCap.

6.7 Bright Light Therapy

Bright Light treatment will consist of 8 weeks of daily use of the Re-timer device. The Re-timer is worn like a pair of glasses and contains light emitting diodes mounted on the lower portion of the frame. The Re-timer emits blue-green 500 nm light with an intensity of ~500 lux lm/m^2. Subjects will be instructed to use the device for 30 minutes within two hours of waking, in the morning. (See appendix for instruction manual).

6.8 Cognitive Behavioral Therapy for Insomnia

CBT-I treatment will receive 1 session every week, for 8 weeks (8 total sessions). The CBT-I sessions will be provided by a pool of clinical PhD psychology students by a trained professional. Each visit will be conducted via telehealth. Sessions will include discussions regarding such topics as sleep restriction, stimulus control and sleep hygiene. Review of sleep diaries will occur during the sessions.

6.9 Standard of Care

Subjects will continue the care they routinely receive.

7. Study Procedures

7.1 Screening Visit

The following procedures will be performed during the screening process:

- Sign and date the informed consent and HIPAA release
- Review of inclusion/exclusion criteria
- Questionnaires: PROMIS Sleep Disturbance & FSS

After screening procedures have been completed and the subject meets eligibility criteria, the research coordinator will randomize the subject based on the randomization scheme described in Section 5.

7.2 Baseline Visit - Day 1

Study subjects will be sent the Actigraph (see appendix for education guidelines) with a prepaid return envelope. Questionnaires and sleep diary will be sent electronically via REDCap. If the subject is randomized to Bright Light Therapy, the Re-Timer Glasses (see appendix for education guidelines) will also be sent.

The Research Coordinator will confirm receipt of actigraph/Re-Timer glasses and confirm understanding of how to wear each device and review the questionnaires and sleep diary. The Research Coordinator will answer any questions the subject has.

The Research Coordinator will:

- Confirm there has been no change in eligibility
- Review demographics and medical history
- Review medications

The devices will be applied on an agreed upon day with the Research Coordinator and the ActiGraph will be worn for 7 days. The Research Coordinator will contact the subject on Day 7 as a reminder to stop wearing the Actigraph and to return it to the study center.

Subjects will be instructed to complete the following procedures on the same day they start to wear the ActiGraph:

- Questionnaires:
  - FSS
  - PROMS Sleep Disturbance
  - ISI
  - emPHasis-10
  - PROMIS® Physical Function Questionnaire
  - CES-D
  - PSQI
  - PROMIS® Dyspnea Questionnaire
- Sleep Diary (see appendix for education guidelines)

After Baseline study procedures are complete, if the subject has been randomized to the Cognitive Behavioral Therapy group, A member of the CBT-I team will reach out to the research subject to set up a time for the therapist to meet with them. After the initial 7-days of actigraphy and sleep diary are complete, CBT-I treatment will be administered in an individual format by a trained therapist. Training and supervision of the study therapists will be conducted by Dr. Jim Findley. Each subject will receive 8 weekly 60-minute CBT-I sessions remotely. During CBT-I treatment, daily sleep diaries will be completed by subjects. After completion of the 8-weeks of CBT-I actigraphy/questionnaires will be repeated.

If the subject has been randomized to the Bright Light Therapy group. The Research Coordinator will follow up with the subject when they receive the ReTimer glasses to go over how to use the glasses.

If the subject is randomized to the Standard of Care group, they will continue with their usual PAH care.

7.3 Treatment Period (CBT-I Group) – Weeks 2 through 8

Subjects randomized to CBT-I and Light therapy will be contacted once a week, for 8 weeks (total 8 visits) for a remote visit.

The following procedures will be performed for the CBT-I group:

- Medication review

- Adverse event review
- Sleep Diary review
- CBT-I Session

The following will be performed on the Light therapy group:

- Medication review
- Adverse event review

7.4 Treatment Period (All Groups) – Week 9

The subject will be contacted via phone for a remote visit. Study subjects will be sent the Actigraph and questionnaires along with a prepaid return envelope prior to this visit.

The Research Coordinator will confirm receipt and understanding of how to wear the Actigraph and review the questionnaires. The Research Coordinator will answer any questions the subject has.

The Actigraph will be applied on the day after receipt (Week 9) and the ActiGraph will be worn for 7 days. The Research Coordinator will contact the subject on Day 7 as a reminder to stop wearing the Actigraph and to return it to the study center.

The following procedures will be performed:

- Medication review
- Adverse event review
- Sleep Diary review, if applicable
- CBT-I Session, if applicable
- Actigraphy Distribution

7.5 End of Treatment (All Groups) – Week 10

The subject will be contacted for a remote visit.

The following procedures will be performed:

- Medication review
- Adverse event review
- Questionnaires:
    - FSS
    - PROMS Sleep Disturbance
    - ISI
    - emPHasis-10
    - PROMIS® Physical Function Questionnaire
    - CES-D
    - PSQI
    - PROMIS® Dyspnea Questionnaire
- Sleep Diary review

7.6 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. Patients my drop out due to fatigue in complying with study procedures or worsened symptoms. They may also be discontinued from the study at the discretion of the Investigator for concurrent illness, AEs, or other reasons deemed to be in the subject's best interest. It will be documented whether or not each subject completes the study.

Subjects who withdraw early will not be asked to return for a final remote visit. For those participants who withdraw from the study, their data will be eliminated from data analysis.

7.7 Subject Compensation

Subjects will be reimbursed for reasonable travel expenses and the inconvenience of the study procedures necessary for participation. We acknowledge that participation in this study is somewhat burdensome due to the time needed to complete procedures associated with the study. The subject will be compensated $25 for completion of the first visit after the baseline assessments are complete and the actigraph is returned. The subject will receive $50 after the follow up assessments are complete and the actigraph is returned. A total of $75 for completion of all study parts.

Reimbursements for participation in the study will be administered using a Greenphire ClinCard, a reloadable prepaid card. There are no fees for making online or in-store purchases, cashing out the card by presenting it to a teller at any major bank, calling the automated system for balance inquires, calling the customer service number and speaking to a live agent, or addition of funds to the card. The following activities will incur a fee to the balance on your ClinCard: 1) not using the card or having funds added to it for more than 6 months will incur a monthly $3 fee. Every time the card is used or funds are added, this 6-month period is reset. 2) ATM withdrawals (fees vary based on location) 3) Requesting a paper statement (instead you can always check your available balance online or by calling Customer Service) 4) Requesting a replacement card through Customer Service will incur a $7.00 fee and take 7-10 days to receive by mail. Instead, if your card is lost, stolen or damaged, contact your study coordinator so that s/he can replace your card at no charge. 5) Requesting a check through Customer Service to remove funds from the card. Please read the ClinCard Cardholder FAQ given to you by the research team.

8. Study Endpoints

8.1.1 Primary Study Endpoint

- The primary endpoint will be the measurement of recruitment and retention rates.

8.1.2 Secondary Study Endpoints

- To compare the effects of CBT-I and Bright Light Therapy to Standard of Care on (insomnia and fatigue severity) and secondary (wake after sleep onset and sleep onset latency) outcomes.
- To test the effects of CBT-I and Bright Light Therapy to Standard of Care on the secondary outcome physical activity.
- To test the effects of CBT-I and Bright Light Therapy to Standard of Care on the secondary outcomes: depression, dyspnea and QOL.

9. Statistical Plan

9.1 Sample Size and Power Determination

We used parameter estimates from an RCT using Bright Light Therapy to improve cancer related fatigue to conduct a sample size calculation for our study.[9] The authors reported mean fatigue severity score (Fatigue Severity Scale) of 9.48 and 14.45 at the conclusion of their study with standard deviations of 16.11 and 15.57. Our calculations indicated that we need a total of 312 subjects to achieve 80% power while maintaining the type I error rate $\alpha = 0.05$. We intend to recruit 10% of subjects required to determine the sample size for an adequately powered RCT in PAH.[44] With an estimated 20% attrition rate from our other study[45] we will enroll 36 subjects to achieve a sample of 30.

9.2 Statistical Methods

We will use intention-to-treat analyses. First, we will calculate the frequencies and percentages for all demographic (e.g. sex) and clinical (e.g. medications) categorical variables and use Fisher's exact test to compare baseline differences between groups. We will obtain means, medians, standard deviations, and interquartile-ranges for all continuous demographic (e.g. age) and clinical variables (e.g. body mass index) and use t- tests to compare baseline differences. between groups. We will use non-parametric tests to compare the groups if the data do not follow normal distribution.

To evaluate Aim 1, we will calculate appropriate descriptive measures for recruitment and retention rates. For Aims 2 and 3 our goal is to compare the three groups. As such we will calculate difference scores (Week 10 – Baseline scores) for our outcome variables (insomnia and fatigue) . To maintain experiment-wise type I error rate at the nominal level ($\alpha = 0.05$), we will conduct an omnibus test for overall differences between the three groups using the ANOVA approach. In the presence of a significant overall difference, we will conduct post hoc comparison of the two treatment conditions with the Standard of Care group using the Dunnett approach. We will verify the assumptions related to the ANOVA using residuals. We will use the non-parametric Kruskal-Wallis approach if the data do not satisfy the normal distribution assumption. If our preliminary analysis identifies group differences at baseline, we will adjust for the difference at baseline and perform analysis of covariance. Analyses will be primarily conducted using the R statistical environment.

10. Safety and Adverse Events

10.1 Definitions

There is a reasonable possibility that the adverse event (AE), experience, or outcome may have been caused by the procedures involved in the research.

10.1.1 Unanticipated Problem (UP)

Any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given
    - a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and
    - b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

10.1.2 Adverse Event (AE)

Any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious AE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

10.1.3 Serious Adverse Event (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening

- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-subject hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

10.1.4 Expectedness

Expected: an AE known to be associated with the intervention or condition under study.
Unexpected: any AE occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is not consistent with either:

- the known or foreseeable risk of AEs associated with the procedures involved in the research that are described in: the protocol-related documents, such as the IRB-approved research protocol and the current IRB-approved informed consent document, and other relevant sources of information; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

10.1.5 Relatedness

Definite: the AE is clearly related to the intervention
Probably: the AE is likely related to the intervention
Possible: the AE may be related to the intervention
Unlikely: the AE is doubtfully related to the invention
Unrelated: the AE is clearly not related to the intervention

10.1.6 Adverse Event Reporting Period

The study period for which AEs must be reported for this study is defined as the period from the initiation of any study procedures to 5 days after the last study visit.

10.1.7 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

10.1.8 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.2 Recording of Adverse Events

At each contact with the subject, the research team will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event case report form (CRF) and electronic case report form (eCRF in REDCap). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the recording period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

10.3 Relationship of AE to Study

The investigator must assess whether the adverse event represents an unanticipated problem following the guidelines described in section 10.1.1 above. If the investigator determines that the adverse event represents an unanticipated problem, the investigator must report it promptly to the IRB.

10.4 Reporting of Adverse Events and Unanticipated Problems

The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm.

A reportable event is an adverse event or incident that has the potential to be classified by the IRB as an unanticipated problem posing risks to participants or others. An incident is determined to be reportable to the IRB when it is both:

1. **probably** or **definitely** related to participation in the research
2. unexpected in terms of nature, severity, or frequency

Events that meet these criteria, must be submitted to the IRB within 10 business days of discovery. However, **if the event involved a death, the investigator should report within 3 calendar days.**

If the event does not meet the reporting criteria above, the following table describes whether the event is reportable to the IRB, and if so, when it should be reported.

Relatedness	Expectedness	Reportable to IRB?	When to Report
Unrelated or Unlikely related	Expected and Unexpected	NO	N/A
Possibly, Probably, or Definitely related	Expected	NO	N/A
Possibly related	Unexpected	YES* ONLY IF: The event suggests that the research places **subjects or others** at greater risk than was previously known or recognized (i.e., changes to the study conduct are required to mitigate risk and/or participants' willingness to participate may be adversely impacted)	EXPEDITED REPORTING WITHIN 10 bus. days Summarize at continuing review
Probably or Definitely related	Unexpected	YES*	EXPEDITED REPORTING WITHIN 10 bus. days Summarize at continuing review
Probably or Definitely related death	Unexpected	YES*	EXPEDITED REPORTING WITHIN 3 calendar days Summarize at continuing review

*Includes serious and non-serious events.

10.4.1 Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the institution required form or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

The Principal Investigator is expected to provide as much of the following information as is available:

- Protocol name and number
- Subject identifiers
- Demographic data
- Nature of the event
- Severity of the event
- Probable relationship (causality) of AE to study procedure
- Date and time of AE onset
- Date and time of AE resolution, if available
- Concomitant medications that the participant was taking for an underlying medical condition or disease and the therapeutic agents used for the treatment of the adverse event
- Clinical assessment of participant conducted at time of SAE/AE
- Results of any laboratory and/or diagnostic procedures, and treatment
- Follow-up plan
- Outcome
- Autopsy findings (if appropriate)

The Principal Investigator and research coordinator will provide details about the AE as they become available. If additional information cannot be obtained for whatever reason, this will be documented.

The Principal Investigator should promptly determine an assessment of causality.

The Principal Investigator/designee should keep originals or photocopies of all relevant documentation, including facsimile confirmations and email exchanges, and file them in the participant's file.

The Principal Investigator/designee should file copies of all correspondence with the IRB in the appropriate section of the Regulatory Master File or site study file.

The Principal Investigator will review all SAEs/Ups for the study.

10.4.2 Follow-up Report

If an AE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAEs are followed until either resolved or stable.

11. Study Administration, Data Handling and Record Keeping

11.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

11.2 Subject Privacy

Potentially eligible subjects will be identified by screening Pulmonary Hypertension clinics at Penn through EPIC. They will be approached about the study via phone. The subject will provide the best number of contact and be given the staff's member card with contact information so that they may call with any questions and to schedule the study visit. The study visit will take place remotely via secured telehealth software.

11.3 Data Collection and Management

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigator will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

Clinical data will be obtained from the patients and their clinical charts. Subjects will be assigned a unique identifier when the screening data are entered. The unique identifier will be linked to the subject name. Only the PI and the research coordinator will have access to the linkage between the subject identity and the unique identifier.

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the PI. All source documents must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems, adverse events, and severe adverse events must be reviewed by the investigator.

This study will use a Redcap database. The database will be hosted on secure computing servers and will be restricted to only those individuals who are authorized to work on the study. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the study. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies.

Source documents will be identified by the subject ID number and other identifiers will be removed or blacked out. All documents (including questionnaires, sleep diaries, subject study binders, etc.) will be kept in a locked file cabinet in a locked room. Identifiers will be stored separately, also in a locked cabinet and/or a password-protected computer.

Protection against the risk of unintended data disclosure will rely on (1) adequate training of study personnel in accordance with NIH human subjects research training policies; (2) study procedures and protocols defining appropriate data management principles; and (3) a secure data management infrastructure. All study personnel involved in the direct collection and analysis of identifiable research data will undergo required training in human subjects' research participant protections as required by NIH. Standards will be formalized among the study team to ensure the maintenance of the study dataset in a single, secure location, and prohibiting transfer of study data to removable or portable media for personal use. Additional procedures will be defined for de-identification of the final study dataset as appropriate for data sharing purposes. No identifiers will be shared, and Data Use Agreements would need to be executed before sharing data.

11.4 Personnel Training

Prior to enrollment of the first subject in the study protocol, the Investigator will ensure that staff has completed appropriate training and that all documentation including IRB approval is completed and available. The purpose of training is to ensure that study personnel are carrying out the protocol in a consistent way and are adhering to good clinical practice guidelines. Staff will have current Human Subjects Training Certification on file. Before enrollment begins, study coordinators and research assistants who will perform the outcome assessments will be trained in all procedures, including completion of case-report forms (CRFs).

The PI and research staff will constitute the first line of monitoring of the safety of the human participants. Surveillance for AEs will consist of questioning subjects about potential AEs at every study visit, having subjects report any adverse event to the study team.

12. Study Monitoring, Auditing, and Inspecting

12.1 Study Monitoring Plan

Connie Ulrich PhD, RN, FAAN will monitor this study. Participants will be assessed for eligibility and adherence. No interim analysis is planned. Once the 36 participants have completed the study, analyses will be conducted. We will make every effort to prevent missing data by carefully explaining how to use, Bright Light Therapy, actigraphy equipment, telehealth visit software and reviewing all questionnaires. Study representatives will be accessible by phone 24 hours/day for questions.

12.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

13. Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

13.1 Risks

There are minimal foreseen risks to participation in this study. The light source of the Re-Timer Glasses technology ranges from 115 to 314 hertz. There is a risk of headache, dry mouth, eyestrain, nausea, and hyperactivity after use, which are unlikely but not considered serious AEs. Skin irritation from use of the actigraphy watch is possible, but not considered a serious AE. Adverse events for CBT-I will be assessed by a checklist of 14 somatic and psychological events. This scale asks subjects to check, from a list, symptoms experienced. Checked symptoms are rated in terms of their interference with daytime functioning (0–4 scale: 'not at all' to 'very much'). Items include: Low mood, Fatigue/exhaustion, Extreme sleepiness, Feeling agitated, Bodily pain, Headache/migraine, Euphoria/intense increase in mood, Reduced motivation/energy, Changes in hunger/appetite, Blurred vision, Dizziness, Feeling irritable.

The other risk is potential loss of confidentiality during data collection and remote visits. In order to minimize this risk, procedures will be in place to maintain confidentiality. Computer based files will only be accessible to study personnel through the use of privileges and passwords. However, the risks of this study to subjects are minimal.

13.2 Benefits

It is not expected that the subject will benefit directly from this research study. The results from the study could be applied in the future to subjects (including those in the study) who stand to benefit from the information.

13.3 Risk Benefit Assessment

There is minimal risk to the participants and there is potential benefit to determining a new way to measure the impact of fatigue using Bright Light Therapy in PAH, the risk/benefit ratio is favorable.

14. Study Finances

This study is financed through an investigator-initiated grant from the Bayer, Corporation.

15. Appendices

Table 1: Study Procedures

	Day -30 to 1	Week 1 Day 1		Weeks 2 → 8	Week 9	Week 10
	Screening	Baseline		Treatment Period		End of Treatment
Informed Consent	X					
Demographics and Medical History Review	X					
Medications Review	X	X		X	X	X
Adverse Events Review	X	X		X	X	X
Insomnia Severity Index (ISI)		X				X
PROMIS® Sleep Disturbance	X	X				X
Fatigue Severity Scale (FSS)	X	X				X
emPHasis-10 Questionnaire		X				X
PROMIS® Physical Function Questionnaire		X				X
Center for Epidemiological Studies-Depression (CES-D)		X				X
PROMIS® Dyspnea Questionnaire		X				X
Pittsburgh Sleep Quality Index (PSQI)		X				X
Sleep Diary		X		X	X	
Actigraphy *(7 days)*		X			X	
Cognitive Behavioral Therapy Visit				X	X	
Re-timer Glasses Education		X				
Re-timer Glasses Wear		X		X	X	
Randomization	X					

Sociodemographic History

Record ID	_____
Date of Birth	_____
Gender	◯ Female ◯ Male ◯ Non-binary
Race	◯ American Indian or Alaska Native ◯ Asian Indian ◯ Chinese ◯ Filipino ◯ Japanese ◯ Korean ◯ Vietnamese ◯ Other Asian ◯ Black or African American ◯ Native Hawaiian ◯ Guamanian ◯ Chamorro ◯ Samoan ◯ Other Pacific Islander ◯ White ◯ Other/Unknown/Refuse to Answer
Ethnicity	◯ Central American ◯ Cuban ◯ Dominican (Republic) ◯ Mexican ◯ Puerto Rican ◯ South American ◯ Other Latin American ◯ Other Hispanic/Latino/Spanish ◯ Ashkenazi Jewish ◯ Unknown/No answer ◯ None of the above
Name of Country where born:	_____
Health Insurance	◯ Yes ◯ No ◯ Refused ◯ Don't Know

Education Level	☐ No schooling ☐ Nursery school to 8th grade ☐ Some high school, no diploma ☐ High school graduate or GED ☐ Some college or university, no degree ☐ Associate Degree ☐ Bachelor's Degree ☐ Master's Degree ☐ Professional Degree ☐ Doctorate Degree ☐ Don't know
Household size (including participant)	_____
Marital Status	☐ Single ☐ Married ☐ Widowed ☐ Divorced
Employment Status	☐ Employed - full time ☐ Employed - part time ☐ Retired ☐ Disabled ☐ Student ☐ Not Employed
Have you smoked at least 100 cigarettes in your lifetime?	○ Yes ○ No - IF NO, skip to Q#6
How old were you when you first started smoking?	_____
Have you smoked cigarettes during the past 30 days?	○ Yes ○ No - IF NO, skip to Q#5
FOR FORMER SMOKERS How old were you when you QUIT smoking cigarettes?	_____
On average, about how many cigarettes a day do/did you smoke?	_____
Have you ever used any other tobacco products? (e.g. cigars, pipes, snuff, chewing tobacco)	○ Yes ○ No
Current NON-SMOKERS ONLY	

During the past year about how many hours per week were in close contact with people when they were smoking? (e.g. in your home, in a car, at work or other close quarters) _____

Have you ever consumed alcoholic beverages?
○ Yes
○ No - IF NO, skip to Q#12

How old were you when you first started drinking alcoholic beverages? _____

Do you currently drink alcoholic beverages?
○ Yes
○ No - IF NO, skip to Q#7

For how many years did you drink alcoholic beverages?

(Do not count times when you did NOT drink alcohol) _____

In the past, which types of alcoholic beverages did you ordinarily drink? (Mark all that apply)
☐ Wine
☐ Beer
☐ Drinks made with hard liquor (e.g. whiskey, ru
vodka, etc)
☐ Other

What was the usual number of drinks you had per week before you stopped drinking alcoholic beverages? _____

Skip to Q#12

(One drink means 1 beer or 1 glass of wine or 1 shot of liquor or 1 mixed drink. Record 0 if less than one drink per week)

For how many years have you been drinking alcoholic beverages? _____

(Do not count times when you did NOT drink alcohol)

During the past 24 hours, how many drinks have you had? _____

In the past month, what is the largest number of drinks you had in one day? _____

IV drug use:Yes ◯
◯ No

Current or past IV drug

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Postmenopausal: ◯ Yes
◯ No

(No menses for 12 months or longer)

Co-Morbidities from History/Electronic Record

_____

Medical clinical History

Record ID

PAH Etiology	◯ Idiopathic PAH ◯ Heritable PAH ◯ Drug and toxin induced ◯ Connective tissue disease ◯ HIV infection ◯ Portopulmonary hypertension ◯ Congenital heart diseases
Heritable PAH types	◯ ALK1 ◯ Endoglin ◯ BMPR2 ◯ Heritable unknown
Drug and Toxin induced types	◯ Anorexigens ◯ Amphetamine ◯ Methamphetamine ◯ Cocaine ◯ Other
Connective Tissue Disease types	◯ Systemic Sclerosis ◯ Systemic Lupus Erythematosus ◯ Mixed Connective Tissue Disease ◯ Rheumatoid Arthritis ◯ Sjorgens Syndrome ◯ Connective Tissue-Other
Congenital Heart Disease Types	◯ Eisenmenger Syndrome ◯ Congenital Shunts-ASD-Repaired ◯ Congenital Shunts-ASD-Unrepaired ◯ Congenital Shunts-VSD-Repaired ◯ Congenital Shunts-VSD-Unrepaired ◯ Congenital Shunts-PDA-repaired ◯ Congenital Shunts-PDA-Unrepaired ◯ Congenital Shunts-TAPVR-Repaired ◯ Congenital Shunts-TAPVR-Unrepaired ◯ Congenital Shunts-TGA-Repaired ◯ Congenital Shunts-TGA-Unrepaired ◯ Congenital Shunts-AVSD-Repaired ◯ Congenital Shunts-AVSD-Unrepaired ◯ Congenital Shunts-Truncus-Repaired ◯ Congenital Shunts-Truncus-Unrepaired ◯ Congenital Shunts-Other-Repaired ◯ Congenital Shunts-Other-Unrepaired
Postmenopausal: (No menses for 12 months or longer)	◯ Yes ◯ No
Co-Morbidities from History/Electronic Record	

WHO Functional Class

Record ID _____

- ◯ I
- ◯ II
- ◯ III
- ◯ IV

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PROMIS SF v1.0 - Sleep Disturbance 8a

Record ID	_____
In the past 7 days I was satisfied with my sleep.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days My sleep was refreshing.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days I had a problem with my sleep.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days I had difficulty falling asleep.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days My sleep was restless.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days I tried hard to get to sleep.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days I worried about not being able to fall asleep.	◯ Not at all ◯ A little bit ◯ Somewhat ◯ Quite a bit ◯ Very much
In the past 7 days My sleep quality was...	◯ Very poor ◯ Poor ◯ Fair ◯ Good ◯ Very good

Fatigue Severity Scale

Record ID	_____
My motivation is lower when I am fatigued.	◯ 1 Strongly disagree ◯ 2 Moderately disagree ◯ 3 Mildly disagree ◯ 4 Neither disagree or agree ◯ 5 Mildly agree ◯ 6 Moderately agree ◯ 7 Strongly agree
Exercise brings on my fatigue.	◯ 1 Strongly disagree ◯ 2 Moderately disagree ◯ 3 Mildly disagree ◯ 4 Neither disagree or agree ◯ 5 Mildly agree ◯ 6 Moderately agree ◯ 7 Strongly agree
I am easily fatigued.	◯ 1 Strongly disagree ◯ 2 Moderately disagree ◯ 3 Mildly disagree ◯ 4 Neither disagree or agree ◯ 5 Mildly agree ◯ 6 Moderately agree ◯ 7 Strongly agree
Fatigue interferes with my physical functioning.	◯ 1 Strongly disagree ◯ 2 Moderately disagree ◯ 3 Mildly disagree ◯ 4 Neither disagree or agree ◯ 5 Mildly agree ◯ 6 Moderately agree ◯ 7 Strongly agree
Fatigue causes frequent problems for me.	◯ 1 Strongly disagree ◯ 2 Moderately disagree ◯ 3 Mildly disagree ◯ 4 Neither disagree or agree ◯ 5 Mildly agree ◯ 6 Moderately agree ◯ 7 Strongly agree
My fatigue prevents sustained physical functioning.	◯ 1 Strongly disagree ◯ 2 Moderately disagree ◯ 3 Mildly disagree ◯ 4 Neither disagree or agree ◯ 5 Mildly agree ◯ 6 Moderately agree ◯ 7 Strongly agree

Fatigue interferes with carrying out certain duties and responsibilities.	◯ 1 Strongly disagree ◯ 2 Moderately disagree ◯ 3 Mildly disagree ◯ 4 Neither disagree or agree ◯ 5 Mildly agree ◯ 6 Moderately agree ◯ 7 Strongly agree
Fatigue is among my three most disabling symptoms.	◯ 1 Strongly disagree ◯ 2 Moderately disagree ◯ 3 Mildly disagree ◯ 4 Neither disagree or agree ◯ 5 Mildly agree ◯ 6 Moderately agree ◯ 7 Strongly agree
Fatigue interferes with my work, family, or social life.	◯ 1 Strongly disagree ◯ 2 Moderately disagree ◯ 3 Mildly disagree ◯ 4 Neither disagree or agree ◯ 5 Mildly agree ◯ 6 Moderately agree ◯ 7 Strongly agree

Insomnia Severity Index

Record ID	_____
Difficulty falling asleep	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Difficulty staying asleep	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Problems waking up too early	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?	◯ 0 Very satisfied ◯ 1 Satisfied ◯ 2 Moderately satisfied ◯ 3 Dissatisfied ◯ 4 Very dissatisfied
How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?	◯ 0 Not at all Noticeable ◯ 1 A little ◯ 2 Somewhat ◯ 3 Much ◯ 4 Very much noticeable
How WORRIED/DISTRESSED are you about your current sleep problem?	◯ 0 Not at all worried ◯ 1 A little ◯ 2 Somewhat ◯ 3 Much ◯ 4 Very much worried
To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood, etc.) CURRENTLY?	◯ 0 Not at all interfering ◯ 1 A little ◯ 2 Somewhat ◯ 3 Much ◯ 4 Very much interfering

Emphasis10

Record ID	_____
	◯ 0 - I am not frustrated by my breathlessness ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 - I am very frustrated by my breathlessness
	◯ 0 - Being breathless never interrupts my conversations ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 - Being breathless always interrupts my conversations
	◯ 0 - I do not need to rest during the day ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 - I always need to rest during the day
	◯ 0 - I do not feel exhausted ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 - I always feel exhausted
	◯ 0 - I have lots of energy ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 - I have no energy at all
	◯ 0 - When I walk up one flight of stairs I am not breathless ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 - When I walk up one flight of stairs I am very breathless

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◯ 0 - I am confident out in public places/crowds despite my PH
◯ 1
◯ 2
◯ 3
◯ 4
◯ 5 - I am not confident at all in public places/crowds despite my PH

◯ 0 - PH does not control my life
◯ 1
◯ 2
◯ 3
◯ 4
◯ 5 - PH completely controls my life

◯ 0 - I am independent
◯ 1
◯ 2
◯ 3
◯ 4
◯ 5 - I am completely dependent

◯ 0 - I never feel like a burden
◯ 1
◯ 2
◯ 3
◯ 4
◯ 5 - I always feel like a burden

PROMIS SF v1.2 - Physical Function 8b

Record ID	_____
Are you able to do chores such as vacuuming or yard work?	◯ Without any difficulty ◯ With a little difficulty ◯ With some difficulty ◯ With much difficulty ◯ Unable to do
Are you able to go up and down stairs at a normal pace?	◯ Without any difficulty ◯ With a little difficulty ◯ With some difficulty ◯ With much difficulty ◯ Unable to do
Are you able to go for a walk of at least 15 minutes?	◯ Without any difficulty ◯ With a little difficulty ◯ With some difficulty ◯ With much difficulty ◯ Unable to do
Are you able to run errands and shop?	◯ Without any difficulty ◯ With a little difficulty ◯ With some difficulty ◯ With much difficulty ◯ Unable to do
Does your health now limit you in doing two hours of physical labor?	◯ Not at all ◯ Very little ◯ Somewhat ◯ Quite a lot ◯ Cannot do
Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	◯ Not at all ◯ Very little ◯ Somewhat ◯ Quite a lot ◯ Cannot do
Does your health now limit you in lifting or carrying groceries?	◯ Not at all ◯ Very little ◯ Somewhat ◯ Quite a lot ◯ Cannot do
Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	◯ Not at all ◯ Very little ◯ Somewhat ◯ Quite a lot ◯ Cannot do

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Record ID _____

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way DURING THE PAST WEEK.

1. I was bothered by things that don't usually bother me.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
2. I did not feel like eating; my appetite was poor.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
3. I felt that I could not shake off the blues even with the help of my family or friends.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
4. I felt that I was just as good as other people.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
5. I had trouble keeping my mind on what I was doing.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
6. I felt depressed.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
7. I felt everything I did was an effort.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
8. I felt hopeful about the future.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)

9. I thought my life had been a failure.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
10. I felt fearful.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
11. My sleep was restless.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
12. I was happy.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
13. I talked less than usual.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
14. I felt lonely.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
15. People were unfriendly.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
16. I enjoyed life.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
17. I had crying spells.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
18. I felt sad.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)

19. I felt that people disliked me.	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)
20. I could not get "going".	◯ Rarely or none of the time (less than 1 day) ◯ Some or a little of the time (1-2 days) ◯ Occasionally or a moderate amount of the time (3-4 days) ◯ Most or all of the time (5-7 days)

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

Score: _____

PROMIS SF v1.0 - Dyspnea Severity 10a

Record ID	_____
Over the past 7 days, how short of breath did you get with each of these activities? Dressing yourself without help	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days
Over the past 7 days, how short of breath did you get with each of these activities? Walking 50 steps/paces on flat ground at a normal speed without stopping	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days
Over the past 7 days, how short of breath did you get with each of these activities? Walking up 20 stairs (2 flights) without stopping	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days
Over the past 7 days, how short of breath did you get with each of these activities? Preparing meals	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days
Over the past 7 days, how short of breath did you get with each of these activities? Washing dishes	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days
Over the past 7 days, how short of breath did you get with each of these activities? Sweeping or mopping	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days
Over the past 7 days, how short of breath did you get with each of these activities? Making a bed	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days
Over the past 7 days, how short of breath did you get with each of these activities? Lifting something weighing 10-20 lbs (about 4.5-9 kg, like a large bag of groceries)	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days
Over the past 7 days, how short of breath did you get with each of these activities? Carrying something weighing 10-20 lbs (about 4.5-9 kg, like a large bag of groceries) from one room to another	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days

Over the past 7 days, how short of breath did you get with each of these activities? Walking (faster than your usual speed) for ?? mile (almost 1 km) without stopping	◯ No shortness of breath ◯ Mildly short of breath ◯ Moderately short of breath ◯ Severely short of breath ◯ I did not do this in the past 7 days

Pittsburgh Sleep Quality Index (PSQI)

Record ID	_____
Subject's Initials	_____
ID#	_____
Date	_____
Time	_____
AM or PM	_____

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?	_____ (BED TIME)
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?	_____ (NUMBER OF MINUTES)
3. During the past month, what time have you usually gotten up in the morning?	_____ (GETTING UP TIME)
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)	_____ (HOURS OF SLEEP PER NIGHT)

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

5a) Cannot get to sleep within 30 minutes	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
5b) Wake up in the middle of the night or early morning	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
5c) Have to get up to use the bathroom	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
5d) Cannot breathe comfortably	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
5e) Cough or snore loudly	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
5f) Feel too cold	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
5g) Feel too hot	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
5h) Had bad dreams	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
5i) Have pain	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
5j) Other reason(s), please describe	_____
How often during the past month have you had trouble sleeping because of this?	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week

6. During the past month, how would you rate your sleep quality overall?	◯ Very good ◯ Fairly good ◯ Fairly bad ◯ Very bad
7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	◯ No problem at all ◯ Only a very slight problem ◯ Somewhat of a problem ◯ A very big problem
10. Do you have a bed partner or room mate?	◯ No bed partner or room mate ◯ Partner/room mate in other room ◯ Partner in same room, but not same bed ◯ Partner in same bed
If you have a room mate or bed partner, ask him/her how often in the past month you have had...	
10a) Loud snoring	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
10b) Long pauses between breaths while asleep	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
10c) Legs twitching or jerking while you sleep	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
10d) Episodes of disorientation or confusion during sleep	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week
10e) Other restlessness while you sleep; please describe	_____
	◯ Not during the past month ◯ Less than once a week ◯ Once or twice a week ◯ Three or more times a week

Adverse Events Symptoms Questionnaire

Record ID

Low Mood	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Fatigue/Exhaustion	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Extreme Sleepiness	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Feeling agitated	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Bodily pain	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Headache/Migraine	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Euphoria/intense increase in mood	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Reduced motivation/energy	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Changes in hunger/appetite	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe

Confidential

Blurred vision	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Dizziness	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe
Feeling irritable	◯ 0 None ◯ 1 Mild ◯ 2 Moderate ◯ 3 Severe ◯ 4 Very severe

Sleep Diary

Name:______________________

	Sample							
Today's date	4/5/08							
In total, how long did you nap or doze yesterday?	n/a							
1. What time did you get into bed?	10:15 p.m							
2. What time did you try to go to sleep?	11:30 p.m							
3. How long did it take you to fall asleep?	1 hour 15 min.							
4. How many times did you wake up, not counting your final awakening?	3 times							
5. In total, how long did these awakenings last?	1 hour 10 min.							
6a. What time was your final awakening? 6b. Did you wake up earlier than you desired? 6c. If yes, how many minutes earlier?	6:35 a.m. ☑ Yes ☐ No 30 min.							
7. What time did you get out of bed for the day?	7:20 a.m							
8. How would you rate the quality of your sleep?	☐ Very poor ☑ Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐Poor ☐ Fair ☐ Good ☐ Very good	☐ Very poor ☐Poor ☐ Fair ☐ Good ☐ Very good
9. Comments (if applicable)	I have a cold							

Sleep Diary Instructions

What is a Sleep Diary? A sleep diary is designed to gather information about your daily sleep pattern.

How often and when do I fill out the sleep diary? It is necessary for you to complete your sleep diary every day. Ideally, the sleep diary should be completed within one hour of getting out of bed in the morning

What should I do if I miss a day? If you forget to fill in the diary or are unable to finish it, leave the diary blank for that day.

What if something unusual affects my sleep or how I feel in the daytime? If your sleep or daytime functioning is affected by some unusual event (such as an illness, or an emergency) you may make brief notes on your diary.

What do the words "bed" and "day" mean on the diary? This diary can be used for people who are awake or asleep at unusual times. In the sleep diary, the word "day" is the time when you choose or are required to be awake. The term "bed" means the place where you usually sleep.

Will answering these questions about my sleep keep me awake? This is not usually a problem. You should not worry about giving exact times, and you should not watch the clock. Just give your best estimat

Item Instructions

Use the guide below to clarify what is being asked for each item of the Sleep Diary.

Date: Write the date of the morning you are filling out the diary

In total, how long did you nap or doze? Estimate the total amount of time you spent napping or dozing, specifying if you are referring to hours or minutes. For instance, if you napped twice, once for 30 minutes and once for 60 minutes, and dozed for 10 minutes, you would answer "1 hour 40 minutes." If you did not nap or doze, write "N/A" (not applicable). *1. What time did you get into bed?* Write the time that you got into bed. This may not be the time that you began "trying" to fall asleep.

2. What time did you try to go to sleep? Record the time that you began "trying" to fall asleep.

3. How long did it take you to fall asleep? Beginning at the time you wrote in question 2, how long did it take you to fall asleep.

4. How many times did you wake up, not counting your final awakening? How many times did you wake up between the time you first fell asleep and your final awakening?

5. In total, how long did these awakenings last? What was the total time you were awake between the time you first fell asleep and your final awakening. For example, if you woke 3 times for 20 minutes, 35 minutes, and 15 minutes, add them all up (20+35+15= 70 min or 1 hr and 10 min).

6a. What time was your final awakening? Record the last time you woke up in the morning.

6b. Did you wake up earlier than you planned? If you woke up or were awakened earlier than you planned, check yes. If you woke up at your planned time, check no.

6c. If yes, how much earlier? If you answered "yes" to question 6c, write the number of minutes you woke up earlier than you had planned on waking up. For example, if you woke up 15 minutes before the alarm went off, record 15 minutes here.

7. How would you rate the quality of your sleep? "Sleep Quality" is your sense of whether your sleep was good or poor.

8. *Comments* Feel free to write anything that you would like to say that is relevant to your sleep.

RE-TIMER™

You will be using your Re-Timer device for 30 minutes within two hours of waking in the morning*

Setting up your Re-Timer

Follow these steps to charge your device:

1) Plug the charging cable into the charging port of your Re-Timer *(A, Diagram 1)*

2) Plug the opposite end of the charging cable into either your computer's USB port or a USB wall adapter.

As the battery charges, the orange LED Battery Indication Light will light up on the display *(B, Diagram 2)*.

This orange light will remain illuminated until the battery is full. If the battery is fully charged the indication panel will remain blank.

When the battery is fully charged it contains enough power to provide up to 5 hours of battery life.

When your Re-Timer is low on battery power the battery indication light will flash red *(B, Diagram 2)*.

Diagram 1: Port for charging cable

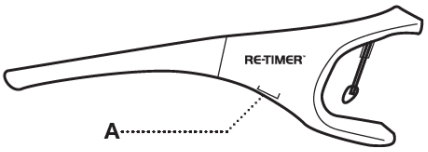
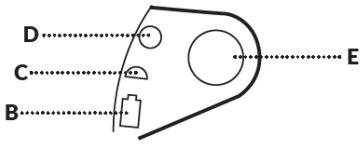


Diagram 2: Indication panel



Warning

You must not use the device while it is charging.

Turning the Re-Timer on and selecting the light intensity setting

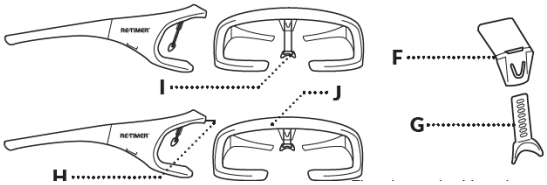


Diagram 3: Adjustable nose piece

Before you place the Re-Timer on your head, turn it on by pressing the control button *(E, diagram 2)* once. This will turn its lights on to the half-brightness setting. If you prefer the full brightness setting, press the control button a second time. You only need to press the button for a moment.

You can see which brightness setting you are using by looking at the control panel. The low brightness indicator *(C, Diagram 2)* will light up when the device is in low brightness mode.

The high brightness indicator will light up when the device is in high brightness mode *(D, Diagram 2)*.

You will be using the high brightness mode.*

Adjusting Re-Timer

Once you have turned your Re-Timer on and selected the high brightness setting, place it on your head. To wear reading glasses while you use your device, put your reading glasses on first, then the Re-Timer. The adjustable nose-piece (Diagram 3) can sit either behind or in front of your reading glasses.

Once the Re-Timer is on your head you can make small adjustments. To move the device closer to or further away from your head slide the top section of the nosepiece (F, Diagram 3) in and out of the frame (H, Diagram 3).

The height of the Re-Timer can be adjusted by the lower portion of the nose-piece (G, Diagram 3). This slides up and down and can be used to accommodate your reading glasses. You can select a low position (J, Diagram 3) or a high position (I, Diagram 3). Adjust the device until it is comfortable.

Tip

Adjust the nose-piece until the light is centered on your eyes. You may use a mirror to assist in aligning the light with your eyes.

Turning Re-Timer off

Once you have finished using your Re-Timer, remove it from your head. Turn it off by pressing the control button (E, Diagram 2). Press the button once if you were using the full brightness setting; twice if you were using the half brightness setting.

Notes

Your eyes must be open when using Re-Timer. Otherwise, you will not receive a therapeutic benefit.

Re-Timer will automatically switch off after 60 minutes of use.

Actigraphy Subject Instructions

Thank you for agreeing to participate in the study. Please read over the following instructions carefully.

What is an Actigraph?
An Actigraph is a motion sensor that records movement to monitor rest/activity cycles. The actigraph measures activity by recording how often and how quickly movements are made. Actigraphs are small, non-invasive devices worn on the wrist and do not interfere with usual daily activities or function.

How do I use the Actigraph?

1. Wear the actigraph all day and night except for showering or bathing so that all of your movement in the day and night is measured.
2. Press the event marker on the actigraph to indicate when you start trying to fall asleep (bedtime) and when you rise in the morning.
3. Wear the Actigraph on your wrist all day.
4. Do not wear the Actigraph during water activities (bathing, showering, swimming) since it is not waterproof.

When should I wear the Actigraph?
The Actigraph will have been programmed to start recording data when you receive it in the clinic. We would like to collect data for 7 days. We will call you on Day 8 to remind you to mail back the actigraph in the stamped, self-addressed envelope we provided you.
Please wear the Actigraph all day and night after you receive the device and wear it continuously (except while swimming or showering).

What happens at the end of the study?
When you take the Actigraph off after day 7 of testing, please put it back in the envelope we provided and mail it back to the study center.

If you have any questions or concerns, please contact:

Lea Ann Matura

matura@nursing.upenn.edu
(215) 746-8819

Thank you for your participation in this study!

1. Edinger JD, Means MK. Cognitive–behavioral therapy for primary insomnia. *Clinical psychology review*. 2005;25(5):539-558.
2. Smith MT, Huang MI, Manber R. Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. *Clinical psychology review*. 2005;25(5):559-592.