BY SIGNING THIS DOCUMENT, THE INVESTIGATOR CONFIRMS:

1. I am not currently debarred by the US FDA from involvement in clinical research studies.
2. I am not involved in any regulatory or misconduct litigation or investigation by the FDA.
3. That if this study involves any funding or resources from an outside source, or if you will be sharing data outside of UVA prior to publication that you will contact the Dean’s office regarding the need for a contract and letter of indemnification. If it is determined that either a contract or letter of indemnification is needed, subjects cannot be enrolled until these documents are complete.
4. The proposed research project will be conducted by me or under my close supervision. It will be conducted in accordance with the protocol submitted to and approved by the IRB including any modifications, amendments or addendums submitted and approved by the IRB throughout the life of the protocol.
5. That no personnel will be allowed to work on this protocol until they have completed the IRB-HSR On-line training and the IRB-HSR has been notified.
6. That all personnel working on this protocol will follow all IRB-HSR Policies and Procedures as stated on the IRB-HSR Website http://www.virginia.edu/vprgs/irb/ and on the School of Medicine Clinical Trials Office Website: http://knowledgelink.healthsystem.virginia.edu/intranet/hes/cto/sops/sop_index.cfm
7. I will ensure that all those delegated tasks relating to this study, whether explicitly or implicitly, are capable through expertise, training, experience or credentialing to undertake those tasks.
8. I confirm that the implications of the study have been discussed with all Departments that might be affected by it and have obtained their agreement for the study to take place.
9. That no subjects will be recruited or entered under the protocol until the Investigator has received the signed IRB-HSR Approval form stating the protocol is open to enrollment.
10. That any materials used to recruit subjects will be approved by the IRB-HSR prior to use.
11. That all subjects will sign a copy of the most current consent form that has a non-expired IRB-HSR approval stamp.
12. That any modifications of the protocol or consent form will not be initiated without prior written approval from the IRB-HSR, except when necessary to eliminate immediate hazards to the subjects.
13. Any significant findings that become known in the course of the research that might affect the willingness of subjects to enroll or to continue to take part, will be promptly reported to the IRB.
14. I will report immediately to the IRB any unanticipated problems involving risk to subjects or to others including adverse reactions to biologics, drugs or medical devices.
15. That any serious deviation from the protocol will be reported promptly to the Board in writing.
16. That any data breach will be reported to the IRB, the UVa Corporate Compliance and Privacy Office, UVa Police as applicable.
17. That the continuation status report for this protocol will be completed and returned within the time limit stated on the form.
18. That the IRB-HSR office will be notified within 30 days of a change in the Principal Investigator or of the closure of this study.
19. That a new PI will be assigned if the current PI will not be at UVA for an extended period of time.
20. Signed consent forms and other research records will be retained in a confidential manner. Records will be kept at least 6 years after completion of the study. These are considered institutional records and may not be
transferred to another institution. A copy of the documents may be taken with the Principal investigator when transferring to another institution.

The IRB reserves the right to terminate this study at any time if, in its opinion, (1) the risks of further experimentation are prohibitive, or (2) the above agreement is breached.

**Investigators Experience**

Karen Ingersoll, Ph.D., will serve as Principal Investigator for this trial. She is an Associate Professor of Psychiatry and Neurobehavioral Sciences at the University of Virginia. Dr. Ingersoll is an experienced clinical researcher with over a decade of consistent funding from NIH institutes including National Institute of Mental Health, the National Institute of Drug and Alcohol; and the National Institute on Alcohol Abuse and Alcoholism. As a clinical health psychologist, she has over 15 years of clinical experience conducting behavioral treatments. Since moving to the University of Virginia, she has collaborated with researchers on new projects to adapt successful behavioral interventions for various technologies including PDAs, mobile phones, and the Internet. She also has a history of working successfully with the other co-investigators on this project (Ritterband, Thorndike, Gonder-Frederick, Cohn) to develop and evaluate other Internet interventions through NIH funded trials, including an Internet intervention for pediatric encopresis and an Internet intervention for improving driving safety among patients with Type 1 diabetes. Dr. Ingersoll is currently leading three NIH-funded grants. In R01AA14356, she is testing a brief motivational intervention to reduce Alcohol Exposed Pregnancy risk among diverse women, and is testing a remote telephone delivery arm. Additionally, she is leading a NIDA R34 to develop and test a text messaging intervention for HIV treatment adherence among rural drug users. In an NIAAA R01, she is coding audiotapes of a completed trial to identify process-outcome relationships that are mechanisms of change in Motivational Interviewing. As PI of the current trial, she will lead the project, convene investigator and operational meetings, and oversee supervision of all staff related to the clinical trial, including the data analyst. She will manage the workload of co-investigators, consultants, and project staff and ensure that implementation and maintenance of the randomized clinical trial, data collection, and data management are proceeding as planned.

Lee Ritterband, PhD: Dr. Ritterband is an Associate Professor at the University of Virginia Health System and Director of the Behavioral Health and Technology (BHT) program area. Over the past 12 years, Dr. Ritterband has established himself as one of the leading researchers in eHealth interventions. He has been a Principal or Co-Investigator on large research projects funded by the National Institute of Mental Health; the National Institute for Childhood Health and Human Development; the National Institute for Diabetes, Digestive and Kidney Diseases; the National Institute of Drug and Alcohol; the National Institute on Alcohol Abuse and Alcoholism; the American Diabetes Association; the Virginia Department of Criminal Justice Services and LifeScan Corporation. He served as Principal Investigator (PI) of the R34 NIMH grant on which the current study is based and was lead author on a paper in Archives of General Psychiatry detailing the findings from that trial. Although Dr. Ritterband is Principal Investigator of the NIMH funded grant connected with this trial, Dr. Ingersoll will serve as the protocol PI to avoid any appearance of conflict of interest in research involving human subjects. This financial conflict of interest is explained below under the Conflicts of Interest section, as well as the Conflicts of Interest Committee decision to accept the proposed management plan of having Dr. Ingersoll serves as protocol PI.

Frances Thorndike, PhD: Dr. Thorndike is an Assistant Professor at the University of Virginia Health System in the Behavioral Health and Technology program area. She has been conducting research in the field of Internet interventions since 2002. Prior to her position at UVA, Dr. Thorndike worked with Dr. Brett Litz at
Boston University on a NIMH trial that tested an Internet intervention to service members with post traumatic stress disorder (PTSD) from the attack on the Pentagon on 9-11 or the Iraq War. At UVA, Dr. Thorndike was a key member on the prior insomnia Internet intervention study on which the current study is based, coordinating the trial and overseeing the day-to-day responsibilities of the study. She is also involved in the development and testing of the other Internet interventions in the BHT lab. Like Dr. Ritterband, Dr. Thorndike has a financial conflict of interest, which is explained in greater detail below.

**Linda Gonder-Frederick, PhD:** Dr. Gonder-Frederick is an Associate Professor in the Department of Psychiatry and Neurobehavioral Sciences and Clinic Director of the Behavioral Medicine Center at the University of Virginia Health System, which houses the Insomnia Clinic. She is an expert in treating patients with insomnia; serves on the Sleep Medicine board at UVA; and gives regular lectures to the Neurology, Pulmonology, and Psychiatry residents, whom she also supervises, in behavioral sleep medicine. In addition, Dr. Gonder-Frederick was a key co-investigator on the R34 study, and has been an integral member of the larger Internet intervention research team, providing content, study design/methodology, and implementation expertise.

**Wendy Cohn, PhD:** Dr. Cohn is an Associate Professor in the Department of Public Health Sciences in the Division of Health Services Research and Outcome Evaluation at the University of Virginia Health System. Her main areas of expertise and interest are in program evaluation, outcomes research, public health, epidemiology, and qualitative research. Dr. Cohn was PI of a research project funded by Anthem Blue Cross Blue Shield of Virginia, which focused on the use of market segmentation to characterize and differentiate information into distinct groups based on specific user characteristics and preferences that impact the optimal delivery of health education materials to consumers. Dr. Cohn is also a co-investigator on another NIH-funded trial evaluating an Internet intervention for pediatric encopresis. She oversaw development of the assessment battery in that trial, designing a comprehensive measure to help predict participant intervention use and treatment outcome. Dr. Cohn will employ these same techniques to develop and test a modified version of the measure to determine if there are specific characteristics that are predictive of use and outcome in the Internet intervention for insomnia.

**Mark Quigg, MD:** Dr. Quigg is an Associate Professor in the Department of Neurology at the University of Virginia Health System. He is also the medical director of the combined EEG, Evoked Potential, and Intensive Epilepsy Monitoring Laboratories as well as director of the Neurological Sleep Laboratories at the University of Virginia. His incorporation of neurology into the pulmonary-based sleep laboratory at the University of Virginia was a key factor in the accreditation of the Sleep Center at the University of Virginia. His clinical practice encompasses epilepsy and sleep, with emphasis on epilepsy surgery in the former and sleep-associated consequences of neurological disease in the latter. His clinical research experience in reference to sleep medicine has examined associations among sleep, circadian regulation, and epilepsy as well as use and effects of polypharmacy in a variety of comorbid conditions.

**Dr. Charles Morin:** Dr. Morin is Professor of Psychology at the University of Laval in Quebec, Canada, and director of their Sleep Research Center. Dr. Morin is considered one of the foremost experts in the field of insomnia. He is a member of the DSM-V Work Group for the Sleep Disorders Section, and is chairing the 2011 meeting of the World Association of Sleep Medicine. He is an associate editor for the journals *Sleep* and *Behavioral Sleep Medicine*, and has published over 150 peer-reviewed articles. He has written several popular and scientific books covering the treatment of insomnia. The UVA team has collaborated with Dr. Morin since 2003, and has an excellent working relationship with the group. The content of the Internet intervention is based on Dr. Morin’s cognitive-behavioral treatment program for insomnia.
Signatures

**Principal Investigator**

<table>
<thead>
<tr>
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<th>Date</th>
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**Department Chair**

BY SIGNING THIS DOCUMENT THE DEPARTMENT CHAIR AGREES:

1. To work with the investigator and with the board as needed, to maintain compliance with this agreement.
2. That the Principal Investigator is qualified to perform this study.
3. That the protocol is scientifically relevant and sound.

<table>
<thead>
<tr>
<th>Department Chair or Designee</th>
<th>Date</th>
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</thead>
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<td>Signature</td>
<td></td>
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<tr>
<td>Name Printed</td>
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</table>

The person signing as the Department Chair cannot be the Principal Investigator or a sub-investigator on this protocol. The Department Chair or Designee signature is ONLY required if this is a new protocol or a modification changing the Principal Investigator
This study will compare the efficacy of an interactive Internet intervention to treat adult insomnia (Sleep Healthy Using the Internet; SHUTi) to that of a static Patient Education (PE) website to improve sleep, mood related symptoms, perceived health status, and overall quality of life. SHUTi is based on cognitive-behavioral treatment (CBT) for insomnia. This NIMH R01 study follows the successful completion a smaller NIMH funded project (R34MH70805), which tested the feasibility and preliminary efficacy of the Internet intervention for adults with insomnia. The current study will test an optimized SHUTi program in a more heterogeneous national sample. More specifically, 300 adults with insomnia will be recruited, including those with comorbid psychological or medical conditions, as part of a 2 (PE vs. SHUTi) X 4 (Pre, Post, 6 and 12 month follow-up) study design. One year follow-up data will be collected to determine whether treatment gains are maintained. We will also assess participants’ access to other insomnia treatments, conduct cost effectiveness analyses, identify user characteristics related to use of the intervention and symptom improvements, and evaluate participants’ acceptance of their respective web programs. Although participants with many comorbid medical and psychological disorders will be included, pregnant women will be excluded because some of the treatment recommendations (e.g., sleep restriction) would not be appropriate during pregnancy.
population reporting insomnia symptoms and 10% to 15% suffering from chronic insomnia. Insomnia may contribute to daytime fatigue, impaired performance, confused thinking and judgment, and difficulty with work and personal tasks. In the 2002 National Sleep Foundation (NSF) “Sleep in America” poll, 37% of respondents stated that they were so sleepy during the day that it disrupted their daily activities at least several days each month. This is confirmed by objective assessment of documented performance errors and increased risk of accidents at work.

In spite of the prevalence of insomnia, few individuals actually receive treatment. Prescribed sleeping medications such as antidepressants, hypnotics, and non-hypnotic benzodiazepines have been found to be an effective, short-term treatment for acute insomnia when compared to placebo-controlled groups. However, it is important to note that pharmacological treatments tend to treat symptoms rather than underlying issues, have possible side effects including drowsiness, dizziness, and cognitive impairments and significant potential for a rebound effect when medication is discontinued.

CBT for insomnia focuses on the maladaptive behaviors and dysfunctional thoughts that perpetuate sleep problems. Among treatments for insomnia, numerous studies have found CBT to be one of the most effective. Comparing psychological and pharmacological treatments has shown that individuals receiving CBT had better long-term clinical gains. CBT can be conceptualized as six Cores of treatment that include behavioral, educational, and cognitive techniques. The Behavioral Cores incorporate sleep restriction and stimulus control; the Educational Core focuses on general education about sleep and improving sleep hygiene; the Cognitive Core attempts to address and change the negative beliefs and thoughts that may exacerbate sleep difficulties; the Overview and Consolidation/Relapse Prevention Cores introduce treatment content and help the patient identify risk situations and use strategies to reduce relapse. The structured nature of insomnia treatment makes it an ideal intervention for adaptation as a Web program and delivered via the Internet.

There are approximately 1,100 accredited sleep centers in the United States. However, there are less than 200 specialists certified in Behavioral Sleep Medicine. Insurance companies do not typically provide coverage for behavioral treatment for insomnia, making it unlikely that CBT for insomnia could become part of standard practice. Most Americans who suffer from chronic insomnia do not have access to psychologically-based treatment. The Internet has become an important source of health care and medical information. As of October 2006, 80% of US adult Internet users had searched for health-related information on the Internet. Clearly, the Internet is playing a role in how people seek medical attention.

A growing minority of sites provides health interventions which patients can use to self-treat or use in conjunction with face-to-face treatment. Outcome trials of Internet interventions have consistently demonstrated significant symptom improvements or changes in behavior. Papers on Internet interventions have been published, including review articles as well as pediatrics, obesity and depression and anxiety. Such Internet health interventions are typically behaviorally-based treatments that have been operationalized and transformed for delivery via the Internet.

An Internet intervention to treat adult insomnia (Sleep Healthier Using The Internet; SHUTi) has been developed. Testing was completed in late 2007, and six-month follow-up data was collected through July, 2008. Forty-four adults with insomnia were randomly assigned to either the Internet intervention group or a wait-list control group. SHUTi participants showed significant improvements for a number of outcome variables, whereas control participants showed no change. Specifically, SHUTi users showed improvements in sleep efficiency, wake time after sleep onset, and number of nighttime awakenings. Insomnia Severity Index (ISI) scores indicate that participants who received SHUTi also showed marked improvement in insomnia severity. Statistically and clinically significant changes were found after using SHUTi.
six-month follow-up indicate that these positive gains were well maintained for SHUTi participants. The current study will expand on the 2008 trial by: 1) including a broader, more heterogeneous sample, 2) comparing SHUTi to a Patient Education (PE) website (rather than a wait-list control), and 3) conducting follow-up assessments for one-year to examine potential maintenance of treatment effects.

### Hypothesis to be Tested

We hypothesize that adults who receive and utilize the Internet intervention for insomnia (SHUTi) will show greater improvements in sleep, mood related symptoms, perceived health status, and overall quality of life compared to those receiving the Patient Education (PE) website. We believe that use of SHUTi will result in greater sleep improvements compared to the PE website at only a moderate increase in costs, resulting in a greater cost effectiveness ratio.

**Aim / Objective 1:**
We hypothesize that SHUTi will be more effective than the PE website at post, 6-month post and 12-month post in terms of sleep, psychological distress, health, and quality of life variables.

**Aim / Objective 2:**
The specific cost effectiveness hypotheses are:
- Use of SHUTi will result in significantly greater efficacy compared to the Patient Education website at only a moderate increase in costs.
- Use of SHUTi will lead to similar clinical improvements to those reported in the literature for face-to-face care but at significantly reduced cost from both the patient’s and provider’s perspective, resulting in a favorable cost-effectiveness ratio.

**Aim / Objective 3:**
The specific treatment acceptance hypotheses are:
- Participants receiving SHUTi will respond more positively than those receiving the Patient Education website on measures of treatment perception (credibility, acceptability, appropriateness of treatment for sleep difficulties, satisfaction) and perceived impact (perceived improvements in symptoms, relationships, functioning).
- Both groups will respond positively to items related to Internet usability and will not report major barriers to using an online intervention.

### Study Design: Biomedical

1. **Will controls be used?**

   ► **YES.** Participants will be randomly assigned to either receive the interactive Internet intervention (SHUTi) or a static Patient Education (PE) website. The PE website will serve as the control condition. The PE website will provide participants with treatment information included in SHUTi, but it will be delivered in a static format, like a typical insomnia focused website, compared to the interactive and tailored SHUTi intervention.
2. **What is the study design?**

This is a 2 (group) by 4 (assessment) RCT evaluating the Internet intervention for insomnia. Eligible participants will be randomly assigned to SHUTi or the PE website. Follow-up assessments occur immediately post intervention (9 weeks from the start of the intervention), as well as 6-months and 12-months post intervention.

Subjects will not be informed of their condition, although participants may recognize which group they are in based on the description of the two web programs in the consent form and their evaluation of the assigned web program (e.g., no tailored elements in the PE website).

The study coordinator and research team will not be blind to study condition.

3. **Does the study involve a placebo? NO**

### Human Participants

<table>
<thead>
<tr>
<th>Ages</th>
<th>21-65</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td>Both</td>
</tr>
<tr>
<td>Race</td>
<td>All</td>
</tr>
</tbody>
</table>

**Subjects- see below**

1. **Provide target # of subjects (at all sites) needed to complete protocol.**

   Based on effect sizes from our previous study and an alpha of p<.05, the minimum number of participants needed to have 80% power in detecting a group difference for each of the primary and secondary variables is 220. Assuming an initial sample of 220 subjects and an attrition rate of 35%, we will need to recruit 297 participants. Rounding up, the sample size is 300 participants total, 150 for each group.

2. **Describe expected rate of screen failure/ dropouts/withdrawals from all sites.**

   We anticipate a 35% attrition rate across the 12 month study: 5% attrition rate between baseline and post-assessment, 15% attrition between post-assessment and 6 month follow-up, and 15% attrition between 6 and 12 month follow-up. This rate of attrition is based on our previous Internet intervention studies.

3. **How many subjects will be enrolled at all sites?**

   300

4. **How many subjects will sign a consent form under this UVa protocol?**

   300

### Inclusion/Exclusion Criteria

1. **List the criteria for inclusion**

   - Age between 21 and 65 years old.
   - Have sleep-onset insomnia and/or sleep maintenance insomnia (>30 minutes for at least 3 nights/week).
   - Have insomnia symptoms lasting at least 6 months.
   - Have an average total sleep time ≤ 6.5 hours.
   - Sleep disturbances (or associated daytime fatigue) cause significant distress or impairment in social, occupational, or other areas of functioning.
   - Have regular access to a computer and the Internet.
• Reside in the United States or are US Citizens living outside the United States.

2. **List the criteria for exclusion**

• Pregnancy
• Report of a physical illness which is deemed active, unstable, degenerative, and/or progressive, such as congestive heart failure, dementia, or acute pain.
• Bipolar disorder as defined by a manic or hypomanic episode or treatment within the past 10 years.
• Severe depression.
• Endorse risk of suicide.
• Endorse alcohol or drug abuse within the past year.
• Presence of another untreated sleep disorders (e.g., sleep apnea, periodic leg movements).
• Have irregular sleep schedules, with usual bedtimes earlier than 8:00pm or later than 2:00am or arising times earlier than 4:00am or later than 10:00am.
• Current psychological treatment for insomnia.
• Initiating psychological treatment within past 3 months.
• Unstable medication regimen (change to schedule or dosage within past 3 months) for a medication regimen thought to impact sleep.
• Residents of another country.

3. **List any restrictions on use of other drugs or treatments.**

We will include participants on medications, including sleep, psychotropic, and non-sleep medications, as well as PRN regimens, provided that the regimen is stable, as defined by a scheduled and unchanged medication dosage for at least 3 months.

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**Statistical Considerations**

1. **Is stratification/randomization involved?**

► YES.

► **IF YES, describe the stratification/ randomization scheme.**

Randomization will be achieved using a random number generator. Equal numbers of participants will be assigned across the two treatment arms. The participants will be blinded to the randomization but, given the description of the two treatment arms in the consent form, it is possible that participants will deduce which treatment arm they are in. The project coordinator will remain blind to the randomization scheme until it is time to randomize participants (after consent, after conducting baseline phone interview). At that point, the coordinator will learn which treatment that participant will receive. Co-investigators will have access to the randomization scheme.

► **IF YES, who will generate the randomization scheme?**

__X__ Other- Co-investigator: Prior to the start of the study, Frances Thorndike, Ph.D., will use a random number generator to develop a randomization scheme that will be used by the project coordinator to assign participants to treatment condition which participants will learn after they complete baseline assessment.

2. **What are the statistical considerations for the protocol?**
Aim / Objective 1: Determining the efficacy of SHUTi versus Patient Education (PE) website.
Endpoints: sleep variables calculated from prospective sleep diary data (primary and secondary sleep variables), other self-reported sleep variables (e.g., Insomnia Severity Index), psychological variables, perceived health variables, and quality of life variables at pre, post, 6 month and 12 month follow-up.

Aim / Objective 2: Determining whether SHUTi has a more favorable cost-effectiveness ratio than the PE website.
Endpoints: The incremental costs required to produce one additional unit of outcome for patients using SHUTi and for patients using the PE website. Separate estimates of cost-effectiveness will be based in turn on provider, participant and societal perspectives.

Aim / Objective 3: To describe subjects’ acceptance of SHUTi relative to the PE website.
Endpoints: subjects’ ratings of credibility, perceived impact, Internet usability, and barriers to Internet treatment.

Exploratory Objective 1:
We aim to begin to quantify the relative contribution and causal flow of user characteristics, website utilization, change mechanisms, and behavioral changes leading to symptom improvement as depicted in our Model of Internet interventions. We will explore whether certain variables (e.g., self-efficacy) appear to be linked to changes in outcome and could potentially serve as mediators of change.

Exploratory Objective 2: To describe the sample’s access to health care, particularly their access to specialty sleep treatment
Endpoints: We will describe the proportion of participants in the sample who 1) have access to insurance coverage; 2) have unmet health care needs; 3) have a usual source of health care; 4) have had contact with a health professional in the last year; 5) have delayed or missed needed medical care because of cost in the last year. We will also collect participants’ zip codes and then determine whether they fall within 25 miles of an accredited Sleep Medicine Center using the search engine on Sleepcenters.org, which lists all accredited sleep centers within various mile ranges from the American Academy of Sleep Medicine.

Interim Analyses:
Interim analyses may be conducted in order to present interim data at conferences, to publish on interim findings (e.g., after the first post evaluation, the evaluation of the respective web programs will be complete and could be presented in a brief report), and to assist with grant writing for purposes of application for additional grant monies. Additionally, checks may be taken to ensure randomization holds and groups are equivalent across the treatment arms.
The groups will not be stratified during randomization. Where groups differ on baseline variables, these variables will be included in the analysis as covariates. In addition, mediating factors in the success of treatment will be considered in the analysis as discussed above. In particular, participants’ use of insomnia treatment strategies outside those of the intervention will be collected and used as covariates in the analyses where appropriate.

Power:
The null hypotheses are that there are no significant differences between groups on the outcomes, while the alternative hypotheses are that the SHUTi group will improve on the outcomes significantly more than the control group. The test statistic will be the interaction effect F, for time by group. The type I error is alpha<.05
and the type II error is beta=.20. With this alpha and beta, the study will have 80% power to address the major endpoints (sleep variables ISI, SOL and WASO). This power calculation is based on effect sizes from our previous study, adjusted downward to reflect that the control group will receive patient education and will likely also improve.

More specifically, sample size determination was made by powering the study to identify differences between pre-post treatment improvements in the PE website and SHUTi. In our previous pilot trial, comparisons between the SHUTi group and wait-list control group resulted in medium to large effect sizes (SOL d=.51; WASO d=1.02; ISI d=1.68). If we used these effect sizes to power this study, sample sizes (based on 80% power and p=.05) would result in estimates of 36, 16, and 8, respectively (see Table 1). However, in the proposed study, we expect that the PE website will have a greater effect on sleep outcomes than placement on a wait-list, resulting in smaller effect sizes. Therefore, in order to estimate effect sizes between groups for the proposed study, we used data collected on the same outcome measures from the Mimeault and Morin’s self-help bibliotherapy trial38 to compare to SHUTi results. We believe there is greater similarity between bibliotherapy and a patient education website in that in both approaches participants are given access to static (typically text) information about insomnia. However, even these estimated effect sizes may be somewhat conservative because it could be argued that bibliotherapy is more likely to improve sleep than Internet patient education because treatment content was administered in a structured and systematic manner (e.g. a specific amount of content delivered in a specific order) over six weeks and contained full chapters on each major insomnia component. Given that this appears to be the best data to use to estimate sample size, Standardized Mean Differences (Cohen’s d) were computed for the results of the bibliotherapy group from the Mimeault and Morin study38 and those who received SHUTi in the previous pilot trial. Differences between the effect sizes for each variable were then used to estimate effect sizes for the proposed study.

Table 1 presents the estimated effect sizes when SHUTi is compared to bibliotherapy.

Taking the highest estimated value of our primary variables (WASO), 220 subjects would be adequate for detecting group differences. We anticipate a 35% attrition rate across the 12 month study. Assuming an initial sample of 220 subjects and an attrition rate of 35%, we will need to recruit 297 participants. Rounding up, the sample size is 300 participants total, 150 for each group.

Table 1. A priori power analysis for sample size

<table>
<thead>
<tr>
<th>Variable</th>
<th>Based on SHUTi outcomes</th>
<th>Based on comparison of SHUTi and Mimeault &amp; Morin results</th>
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<tbody>
<tr>
<td></td>
<td>Est. ES d</td>
<td>Min. #Ss, 80% Power, p&lt;.05</td>
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<tr>
<td><strong>Primary Variables</strong></td>
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<tr>
<td>ISI</td>
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<tr>
<td>SOL</td>
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<tr>
<td>WASO</td>
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<td><strong>Secondary Variables</strong></td>
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<td>Total Sleep Time</td>
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<tr>
<td># of Awakenings</td>
<td>.80</td>
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**Missing Data:**

We will use mixed-effects analysis to examine time by treatment interactions. Questionnaire data will be “rejected” (not included in analyses) if it is submitted more than two months from its due date. Diary data for a given assessment point will not be included if there are fewer than 7 diary entries within a 14 day period. The relatively unbiased handling of missing data with the mixed effects approach under Missing At Random
assumptions is often listed as one of the primary benefits of mixed models versus repeated measures ANOVA\textsuperscript{36}. With this approach, all data points (that have not been rejected as specified above), including relevant covariates, will be used in computing outcome statistics, without need for imputation of data at missed timepoints. Mixed affects analysis is frequently used to handle missing data in studies of this kind\textsuperscript{37}.

\textit{Note}: See Appendices of Measures to review specific end points individually.

\textbf{3. Do you have an adequate sample size, or is your sample size larger than necessary?}

We based our sample size on effect sizes from our previous pilot study with this Internet delivered intervention for insomnia, using an alpha of $p<.05$ and $80\%$ power in detecting a group difference for each of the primary and secondary variables. Those calculations result in sample of 220 subjects. With the projected attrition rate of $35\%$, we will need to recruit 297 participants. Rounding up, the sample size is 300 participants total, 150 for each group.

The expected study duration is through April 1, 2015. Each participant is enrolled for 12 months.
## Recruitment Milestones for grant serial 86758

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<td>Apr 1</td>
<td>Aug 1</td>
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<td>Target: Hispanic Ethnicity Recruitment</td>
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</tbody>
</table>
4. What is your plan for primary variable analysis?

The efficacy of SHUTi will be assessed by conducting a 2 (group) by 4 (assessment time points) mixed-design ANOVA analysis to identify statistically significant differences between the groups in their change over time on each outcome variables. Group, time, and interaction effects will be assessed and decomposed.

5. What is your plan for secondary variable analysis?

Aim/Objective 1: The efficacy of SHUTi with respect to the secondary sleep, mood, fatigue, and quality of life variables will also be assessed by conducting a 2 (group) by 4 (assessment time points) mixed-design ANOVA analysis to identify significant differences between the groups in their change over time on each secondary outcome variable. Group, time, and interaction effects will be assessed and decomposed.

Aim/Objective 2: The incremental cost effectiveness of SHUTi versus the Patient Education Website will be computed. Cost-effectiveness of the SHUTi intervention will be expressed as the incremental cost required to produce one additional unit of outcome relative to the PE website. We will calculate the incremental cost-effectiveness of SHUTi vs. the PE website by dividing the difference in the average cost per participant of the two web programs by the difference in the average participant outcomes. Additionally, we will quantify a cost-effectiveness ratio where the outcomes are expressed in Quality Adjusted Life Years (QALYs).

Aim/Objective 3: We will conduct one-way analyses of variance and chi-square tests to determine differences between groups in acceptance of their online intervention (for example, perceived impact, usability of the intervention).

Exploratory Objective 1: We will test variables hypothesized to mediate the efficacy of the treatment in order to determine the most important causal mechanisms leading to improved outcomes. To do this we will compare the time (treatment) effects before and after adding mediating variables (e.g., website utilization, behavioral changes), using a linear mixed model approach.

Exploratory Objective 2: We will summarize responses about subjects’ access to health care and estimate the proportion of those with limited access to treatment.

Based on whether any group differences are present at baseline, covariates will be included in the above analyses as appropriate. We will also track participants’ use of insomnia treatment strategies outside of the assigned intervention and include these variables (other treatments used for sleep) as covariates where needed.

Although the power of this study to address secondary objectives varies by variable, there is at least 80% power of detecting a significant (p<.05) pre-post change in the experimental group for most secondary variables. The one exception is the quality of life variable, SF-12 Physical. Based on the pre-post experimental group effect size of d=.15, there will only be about 43% power to find a significant effect on this variable.
Biomedical Research

1. What will be done in this protocol?

Screening:
- Interested individuals across the United States will visit our study website and read the description of the study, including a list of inclusion/exclusion criteria. They can also download a copy of the consent form.
- Before the potential subject continues further he/she will be prompted to read and digitally sign a HIPAA Authorization Stand Alone Form: “Confidentiality, Use and Disclosure of Health Information for Research Purposes.”
- Motivated individuals will then complete the brief online interest form. The form consists of questions regarding contact information, demographics, descriptives, sleep patterns (e.g., how long it takes to fall asleep, number and length of awakenings, quality of sleep, sleep duration) and willingness to participate in study requirements.
- The study coordinator will email ineligible individuals to inform them that they do not qualify for the study. This will typically occur within 48 hours of receipt of online interest form but may take up to 7 days depending on response to recruitment efforts.
- The study coordinator will invite seemingly eligible individuals to complete a phone call where additional details about the study will be provided. If the individual is still interested in participating, the coordinator will provide a detailed review of the electronic consent document and electronic consent procedure during the phone call. This will typically occur within 48 hours of receipt of online interest form but may take up to 7 days depending on response to recruitment efforts.
- Eligible and willing individuals will view the online consent form during the phone call with the study coordinator. After all questions are answered, the eligible participant submits the consent form electronically with a digital signature.
- Submitted consent forms will then be electronically stamped with a time and date as well as the study coordinator’s signature. The signed and dated copy is e-mailed back to the participant, and an electronic version of the consent form is saved in our HIPAA compliant database.
- After the informed consent process is complete, a semi-structured phone interview is completed to collect additional baseline data. Prior to conducting the phone interview, participants will be told that both the interview and subsequent online Assessment Questionnaires include questions about mental health, depression, and use of substances, including alcohol, nicotine, and other substances.
- If the participant is deemed ‘not eligible’ following the phone interview, the individual will be notified and tagged as ‘not eligible’ and why in our electronic database.

Pre-Assessment
- As indicated above, some baseline data is collected during the semi-structured phone interview and will be used as part of the pre-assessment evaluation.
- The Mini-International Neuropsychiatric Interview \(^{34}\) will be administered during the telephone interview to evaluate the presence of certain current and past psychiatric disorders. If a participant meets criteria for Current Major Depressive Episode on the MINI, the interviewer will then conduct the Quick Inventory of Depressive Symptoms-Clinician rated (QIDS-C16) \(^{35}\).
- A clinical psychologist on the team will follow up with any participant who meets the following criteria on the MINI or QIDS-C16: severe depression, moderate to high levels of suicidality, current manic or hypomanic episode, or current substance abuse or dependence. These individuals will be excluded from the
trial, but a clinical psychologist will phone these participants, conduct additional clinical evaluation, and then take the necessary clinical action.

- Following the phone interview, participants are sent login information and study instructions via e-mail.
- When participants first log in to the study website, they will be instructed to complete a ‘How to use this program’ tutorial, that explains how to complete the pre-assessment questionnaire online, as well as instructions on how to complete daily online sleep diaries for two weeks (10 diaries in a 14 day period).
- Following completion of the tutorial, all participants are asked to complete the Pre-Assessment Questionnaire. It is estimated that the Pre-Assessment Questionnaire will take 1½ hours. Participants will receive daily e-mail prompts to complete the Pre-Assessment Questionnaire until it is complete, or until three days have passed since their enrollment date. Participants are able to complete the Questionnaire in more than one sitting as the program auto saves where they are in the Questionnaire. Participants are able to review and revise answers up until the point they select “Submit.” Once the Questionnaire data is submitted, participants no longer have access to their responses on the Questionnaire.
- After the Pre-Assessment Questionnaire is complete, the program automatically advances participants to the Diary phase. Participants are instructed to enter daily sleep diaries for two weeks. It is expected that diary entry will take 2-3 minutes daily. Participants will receive daily e-mail prompts to complete the sleep diaries. Participants are able to review their responses on the Sleep Diary at any time, but they are not able to revise their answers once they select “Submit.”
- After participants submit 10 sleep diaries within a 2 week period, they will automatically gain access to their randomly assigned treatment arm: Patient Education (PE) website or SHUTi.

Intervention

Participants assigned to the **PE group**:
- Will be granted access to log on and securely access the PE website.
- Will have access to the PE website for an entire year during which time they will be able read the static information as frequently as desired.
- The content of the Patient Education website contains static information about insomnia symptoms; diagnosis and differential diagnosis of insomnia; etiology, the natural history of insomnia and its prognosis; and cognitive-behavioral treatment strategies.
- Will receive two reminder e-mails, three and six weeks from completing the Pre-Assessment, indicating how much time is left until they will need to complete the Post-Assessment Questionnaire and Daily Diaries.

Participants assigned to the **SHUTi group**:
- Will be granted access to log on and securely access the SHUTi program.
- Will have access to SHUTi for an entire year during which time they will be able to use this Internet intervention as frequently as desired.
- Will be asked to complete six cores (main intervention content) during the 9 week intervention period (a new Core becomes available 7 days after completion of the previous one). After completing a Core, they can review that Core at any time, and access program worksheets from the My Stuff section of the web program.
- The six cores are based on the primary treatment components provided in face-to-face cognitive-behavioral therapy for insomnia. The Behavioral Cores incorporates sleep restriction\(^{19}\) and stimulus control\(^{20, 21}\), providing patients with a variety of “rules” to follow in order to retrain their bodies to associate sleep with bed. Stimulus control aims to reduce the anxiety or conditioned arousal individuals
may feel when attempting to go to bed. Sleep restriction is a form of systematic mild sleep deprivation in which a sleep window is maintained to allow the body to relearn proper sleeping dynamics and increase sleep efficiency. The Educational Core (also called Sleep Hygiene) focuses on general education about sleep (e.g., understanding the different types of sleep problems) and improving sleep hygiene and other maladaptive behaviors (e.g., establishing regular sleeping schedules, eliminating napping, and avoiding nicotine, caffeine, exercise, and drinking alcohol before bedtime). The Cognitive Core (also called Cognitive Restructuring) attempts to address and change the negative beliefs and thoughts about sleep that may exacerbate sleep difficulties. In addition to these main Cores, there are two other Cores: the Overview and Consolidation/Relapse Prevention Cores. These are critical for each user to receive in order to introduce intervention content and provide a rationale for the intervention (Overview); and integrate the educational, behavioral, and cognitive elements, promote adherence, generalize the information, help the user identify risk situations, and incorporate strategies to reduce relapse (Relapse Prevention).

- A Core is expected to take 45 – 60 minutes to review online. Reviewing and implementing program recommendations will take most participants 30 – 45 minutes per week. Thus, in total, participants in the SHUTi group should expect a time commitment of up to 12 hours, total.
- Although there is some overlap with the PE website and SHUTi, the SHUTi program differs from the PE website in important ways. SHUTi includes: (1) Individually tailored recommendations based on user input of symptoms; (2) High levels of interactivity to increase user engagement (e.g., quizzes, games, online diary entries); (3) Structured implementation of the intervention through the use of metered (distributed) content over the intervention period rather than content presented all at once; and (4) Provision of comprehensive content rather than more general educational information.
- Will receive automated email prompts to encourage users to return to the site.
- Will be encouraged to keep regular online sleep diaries throughout the intervention period.

Post-Assessment
- At the end of the 9 week intervention period, all participants will be instructed (by email) to complete the online Post-Assessment, which consists of one online questionnaire and 10 daily online sleep diaries. The Post-Assessment Questionnaire is estimated to take 1 hour and each diary entry is estimated to take 2-3 minutes. As was true for the Pre-Assessment, participants are able to complete the Post-Questionnaire in more than one sitting as the program auto saves where they are in the Questionnaire. Participants are able to review and revise answers up until the point they select “Submit.” Once the Questionnaire data is submitted, participants no longer have access to their responses on the Questionnaire. For the Sleep Diary, participants are able to review their diary responses at any time, but they are not able to revise their answers once they select “Submit.”
- After completing the Post-Assessment Questionnaire, individuals will have continued access to their online website.
- This same assessment (questionnaires plus diaries) will be completed again at 6 month and 12 month Post-Assessments. It is estimated that the 6 and 12 month Post-Assessments will also take 1 hour and that diary entry will again take 2-3 minutes daily.
- All participants will receive two reminder e-mails for each approaching Post-Assessment.
Measures Timeline

<table>
<thead>
<tr>
<th>Measures</th>
<th>Prior to Pre-Assessment</th>
<th>Online Pre-Assessment</th>
<th>Online Post-Assessment</th>
<th>Online 6-month Post-Assessment</th>
<th>Online 12-month Post-Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Online Interest Form (Inclusion/Exclusion)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phone Screen and Interview</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Online Pre-Assessment Questionnaire</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Online Daily Sleep Diaries (10)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Online Post-Assessment Questionnaire</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

2. Will any of the NON-RADIOLOGIC treatments/procedures be done for research purposes only?

- **YES**, participants will use SHUTi or PE website for 9 weeks and complete assessments prior to starting their assigned web program and 9-weeks, 6-months, and 12-months after, to determine the efficacy of SHUTi with respect to sleep variables, psychological distress, and general health variables.

- **IF YES, (examination(s) are performed for research) check one of the following two options:**
  - **X** The examination(s) utilize(s) the same techniques, equipment, etc., that would be used if the subject were to have the examination(s) performed for clinical care. There exists the potential for the discovery of clinically significant incidental findings.
    - The PI takes full responsibility for the identification of incidental findings:
    - The PI will inform the subjects of all incidental findings that are of clinical significance or are of questionable significance.
    - A follow-up letter describing the finding should be provided to the subject with instructions to either show the letter to their PC or if the subject has no PCP, the subject should be instructed to make an appointment at UVa or at the Free Clinic.
  - **X** This examination(s) utilizes non-standard/investigational, equipment, etc. It is impossible to determine the significance of such results, therefore abnormalities will not be shared with the subject because the meaning of the exam is not yet proven and is of unknown clinical benefit.

3. Will any RADIOLOGIC treatments/examinations be performed for research purposes only? NO

4. If a potential subject does not meet the inclusion/exclusion criteria will you repeat any of the screening procedures/tests? NO

5. If the study involves drawing blood, will the blood be drawn from a central or arterial line?
   The study does not involve blood draws.

6. Will you be using viable embryos? NO
7. **Will you be using embryonic stem cells?** NO

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**Data and Safety Monitoring Plan**

This study has been deemed minimal risk. **Adverse events and serious adverse events will only be collected or recorded if they are deemed related or possibly related to the study intervention.** If any adverse event is considered serious and unexpected, the event must be reported to the IRB-HSR within 7 days from the time the study team receives knowledge of the event.

1. **Definitions**

1.1 How will you define adverse events (AE)?

An adverse event will be considered any undesirable sign, symptom, accident, or medical condition considered **related or possibly related to the intervention.** Medical condition/diseases present before starting the intervention will be considered adverse events only if they worsen after starting the study and that worsening is considered to be related to the study intervention. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

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

1.2 How will you define an unanticipated problem?

An unanticipated problem is any issue that involves increased risk(s) to participants or others. This means issues or problems that cause the subject or others to be placed at greater risk than previously identified, even if the subject or others do not incur actual harm. For example if a subject’s confidentiality is compromised resulting in serious negative social, legal or economic ramifications, an unanticipated problem would need to be reported. (e.g. serious loss of social status, loss of job, interpersonal conflict.)

1.3 What is the definition of a protocol violation?

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the IRB-HSR prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVa staff. These protocol violations may be major or minor violations.
1.4 What is the definition of a data breach?

**Do not change this answer**

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

Additional Information may be found on the IRB-HSR Website: Data Breach

2. What risks are expected due to the intervention in this protocol?

<table>
<thead>
<tr>
<th>Expected Risks related to study participation</th>
<th>Occurrence Rate:</th>
</tr>
</thead>
<tbody>
<tr>
<td>There is a small risk that breaches of privacy and/or confidentiality might occur. The risk of violation of subject privacy and confidentiality is minimal due to the requirements of the privacy plan in this protocol.</td>
<td>Occurs rarely</td>
</tr>
<tr>
<td>Internet concerns: Although some adults may feel more comfortable providing information over the Internet, others may feel less comfortable with this process and have concerns about the confidentiality of their digital data.</td>
<td>Occurs infrequently.</td>
</tr>
<tr>
<td>Discomfort answering questions of a personal nature.</td>
<td>Occurs infrequently.</td>
</tr>
<tr>
<td>Increased tiredness due to restricted time in bed (this is part of the behavioral treatment for insomnia)</td>
<td>Occurs frequently</td>
</tr>
</tbody>
</table>

We will protect against the potential risks to subjects in the following ways:

**Initial discomfort/embarrassment:** During this study, participants will be asked questions of a sensitive and personal nature (e.g., medical history, depressive symptoms). This may cause emotional discomfort in responding. Although we have been unable to identify any negative effects associated with administration of similar interviews and questionnaires used in our previous Internet intervention studies, we will attempt to minimize this risk by asking these questions over the Internet, which may increase sense of anonymity, or by staff trained to be both sensitive and responsive. Confidentiality will be maintained at all times, and no information will be disclosed to another party without the participant’s signed written consent.

**Breach of privacy concerns:** Although some participants may feel more comfortable providing information over the Internet, others may feel less comfortable with this process and have concerns about the confidentiality of their data. To address this concern, data collected through the Internet will be obtained through secured means and stored on our private servers. All data on our servers are password protected and limited to authorized research personnel. Obviously, HIPPA rules are an issue with protecting patient data, and the fact that the system relies on email reminders for users taking the surveys means that some identifying information must be stored in the application. The high-level architecture of the system, however, allows us to separate all other identifying and non-identifying data. We have worked out a system given our previous Internet intervention studies in which two servers have been set up with one private server configured behind the firewall where secured data resides and only individuals who have access onsite are able to connect to this server. A second server maintains the front-end Web system so that individuals (the participants) offsite can access the system.
Data submitted by these users are captured and transferred to the secure server. Analyses will be conducted without identifiers.

**Initial tiredness:** Participants receiving the SHUTi program will be asked to restrict sleep at certain times, which could lead them to feel initially more tired. To minimize the risk associated with sleep restriction, the system does not recommend participants restrict sleep fewer than five hours. The initial assigned sleep window is also comparable to how much total sleep time the subject gets (based on diary data), but the sleep time is restricted to a smaller window. That is, rather than allowing a participant to get 6 hours of sleep while spending 8 hours in bed, a participant may be asked to spend only 6 hours in bed. To further minimize risks associated with sleep restriction, we will instruct participants that they may contact us if they have significant concerns. Based on the situation, we will provide recommendations, including changing their sleep window or incorporating naps. Participants will also be told to avoid operating a car or other heavy machinery when they feel tired. As needed, we will instruct participants to contact their primary care provider or seek professional help at a sleep clinic.

**Anticipated Adverse Events**

Adverse events deemed Related or Possibly Related will be collected and reported to the IRB. As explained in detail above, the following risks/adverse events are anticipated to occur during this study:

1. **Initial discomfort/embarrassment:** During this study, participants will be asked questions of a sensitive or personal nature (e.g., medical history, psychological functioning), which potentially could cause some discomfort or embarrassment in answering these type of questions.

2. **Internet concerns:** Although some adults may feel more comfortable providing information over the Internet, others may feel less comfortable with this process and have concerns about the confidentiality of their digital data.

3. **Initial tiredness:** Participants may be asked to restrict sleep at certain times, which could lead them to initially feel more tired.

**Possibly Related Serious Adverse Events**

Serious adverse events deemed Related or Possibly Related will be collected and reported to the IRB. As indicated above, sleep restriction may frequently result in increased tiredness, which is not deemed to be significant. There are, however, more serious events that could be connected to the “tiredness” caused by sleep restriction. These events are low-probability events, and it will be difficult to determine whether those more serious events are related to the sleep restriction component or more generally related to the fatigue and tiredness typically experienced by adults with insomnia.

Serious Anticipated Events Deemed **Possibly Related** to Study

1. Fatigue-related accidents (e.g., motor vehicle, work related accidents).

3. **When will recording and reporting of unanticipated problems/adverse events begin?**
   
   **X** After subject signs consent

4. **When will the recording/reporting of unanticipated problems/adverse events end?**
   
   **X** Subject completes participation in the protocol

5. **What is your plan for safety monitoring?**

   [Do not change this answer]
Safety monitoring and aggregate review of adverse events, unanticipated problems, protocol violations and any data breach will be performed by the PI and IRB-HSR through continuation review at least annually.

For additional security measures, we will establish a data safety monitoring board (DSMB) following NIH guidelines set forth regarding DSMBs to ensure that the DSMB’s responsibilities are commensurate with the risks, complexity, and nature of our study.

Membership: Our DSMB will be comprised of experts in diverse scientific disciplines, outside of the grant investigators, to ensure participant safety and help interpret the data in our studies. More specifically, our DSMB will consist of:

1. A DSMB Chairperson with expertise organizing and running DSMB meetings (Tracey Hoke, M.D., member of the Patient Safety Committee at UVA Health System)
2. A clinician with expertise in insomnia (Chris Winter, M.D.)
3. A biostatistician (Marc Breton, Ph.D.)
4. An expert in evaluation of Internet delivered treatments (Britt Klein, Ph.D.)

Meetings: Prior to implementation of the study, the DSMB will meet to review the consent and protocol, making recommendations for any needed changes. For this meeting, study investigators will be on hand to answer any specific questions. After the initial meeting, the DSMB will plan to meet annually and prepare an annual report to be submitted to the PI. The PI and study team will then review DSMB recommendations outlined in the Annual DSMB Report and submit a copy of the DSMB report to the IRB. This report will be submitted as a separate report (i.e., not as part of a Continuation). At that time, the UVA study team will also submit to the IRB proposed changes (if needed) to the Protocol and Consent as requested by the DSMB.

DSMB members will have the ability to request more frequent reviews or meetings at any time during the study if they determine such reviews could help ensure patient safety or data integrity. The DSMB will typically meet in "closed session," but they may periodically ask study investigators to attend a meeting to provide additional details on the implementation or conduct of the trial or other pertinent information. After its initial meeting, the DSMB will review the implementation and progress of the study, evaluating study data in either individual or aggregate form to detect evidence of significant benefit or harm for subjects while the trial is in progress. This latter review, beyond that provided by the IRB, serves as a means of additional human subject protection. It does not supplant the regulatory requirement for the principal investigator to report serious and unanticipated adverse events to the local IRB and NIH project officer.

6. What is your plan for reporting a Unanticipated Problem, Protocol Violation or Data Breach?

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>To whom will it be reported:</th>
<th>Time Frame for Reporting</th>
<th>How reported?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated Problems that are not adverse events or protocol violations This would include a Data</td>
<td>IRB-HSR</td>
<td>Within 7 calendar days from the time the study team received knowledge</td>
<td>Unanticipated Problem report form.</td>
</tr>
</tbody>
</table>
### Protocol Violations

(The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)

Or

**Enrollment Exceptions**

Within 7 calendar days from the time the study team received knowledge of the event.

Protocol Violation and Enrollment Exception Reporting Form

*Go to 3rd bullet from the bottom.*

### Data Breach of Protected Health Information

The UVa Corporate Compliance and Privacy Office

*As soon as possible and no later than 24 hours from the time the incident is identified.*

UVa Corporate Compliance and Privacy Office- Phone 924-9741


Police: phone- (434) 924-7166

### DSMB/DSMC Reports

IRB

15 calendar days of the study team receiving the report

Copy of DSMB/DSMC report

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**Payment**

1. Are subjects being reimbursed for travel expenses? **NO.**

2. Are subjects compensated for being in this study? **YES**

2a. What is the maximum TOTAL compensation to be given over the duration of the protocol?
$200

2b. Explain compensation to be given.
Participants will be paid up to $200 for completing all assessments in this study. After completion of the initial post-assessment (9 weeks after starting the study), they will be sent a $50 gift card. After completion of the post-assessment at six months, they will be sent another $50 gift card. After completion of the post-assessment at one year, they will be sent a $100 gift card. All gift cards will be sent via email.

2c. Is payment pro-rated?
► YES, subjects will be emailed a link to their gift card after completing each assessment.

3. Is money paid from UVa or State funds (including grant funds)? YES

3a. How will the researcher compensate the subjects?

► X Gift card

3b. Which category/categories best describes the process of compensation?

► X Compensation will include an alternative method (petty cash, gift card, other) BUT tax information will be collected.

► If an alternate method will be used justify why you are unable to issue checks through the UVa Oracle or state system.

Behavioral Health and Technology (BHT) studies typically use online gift card incentives given the online nature of our studies and the fact that we do not meet with participants face-to-face. Given that we typically use online gift card incentives (Giftcertificates.com), we have administrative procedures in place to efficiently handle gift card incentives to participants and track receipt and use of such cards. Providing participants with gift cards allows for improved tracking of payment and fits with the web-based nature of our research trials.

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Risk/ Benefit Analysis

1. What are the potential benefits for the participant as well as benefits which may accrue to society in general, as a result of this study?

PE Website: Participants assigned to the Patient Education website may learn information about the diagnosis and symptoms of insomnia, its etiology, methods of monitoring sleep, and general treatment strategies. This information is presented through static web pages.

SHUTi: Participants assigned to the SHUTi program receive an interactive intervention designed to primarily improve sleep and secondarily improve mood / psychological distress, quality of life, and perceived health status.

Society: The potential benefits to the adult insomnia community are that this system, and possible future systems like it, would allow for a greater number of individuals to have access to a less expensive and
empirically validated treatment for insomnia. It could potentially reduce health disparity by providing treatment that has not previously been available to patients in more remote areas where access to a behavioral medicine sleep specialists is limited.

2. Analyze the risk-benefit ratio.

Benefit/Risk Ratio. We are balancing the risk of discomfort in answering personal questions, risk of breach of privacy and confidentiality, and risk of increased sleepiness during sleep restriction for the SHUTi participants against developing a treatment for insomnia that could potentially reach greater numbers of affected adults at a reduced cost.

There is appreciable potential for benefit for individuals with insomnia in terms of sleep, psychological distress, and health variables. There is also a potential benefit for larger insomnia community (and those doing research with this community).

The risk associated with breach of privacy and loss of confidentiality is low. Data collected through the Internet will be obtained through secured means and stored on our private servers. All data on our servers are password protected and limited to authorized research personnel. The high-level architecture of the system, however, allows us to separate all other identifying and non-identifying data. We have worked out a system given our previous Internet intervention studies in which two servers have been set up with one private server configured behind the firewall where secured data resides and only individuals who have access onsite are able to connect to this server. A second server maintains the front-end Web system so that individuals (the participants) offsite can access the system. Data submitted by these users are captured and transferred to the secure server. Analyses will be conducted without identifiers.

The risk benefit ratio is acceptable.

Bibliography


**APPENDIX: Sponsor**

**Sponsor Information**

The study is funded by the NIH, National Institute of Mental Health.
APPENDIX: Non-UVA Personnel

1. Explain the duties of non-UVA personnel on this protocol.

Dr. Charles Morin is considered one of the foremost experts in the field of insomnia. He is the PI of several NIH funded studies examining the treatment of insomnia and is a critical member of this research team given his extensive sleep research experience. We have collaborated with Dr. Morin since 2003, and based the content of our earlier version of the insomnia Internet intervention on Dr. Morin’s cognitive-behavioral treatment program for insomnia. For the current study, he will oversee all content revision during Year 01. He will also assist in study design and implementation. In Years 02 and 03, Dr. Morin’s responsibilities will include assisting Dr. Ingersoll with oversight of the intervention and subject recruitment. During Years 04 and 05, Dr. Morin will play an active role in reviewing data, manuscript preparation, and grant progress reports/renewal efforts. These efforts are expected to take 1.2 Person Months (10%) annually.

2. Explain your plans for training and oversight of these personnel.

Dr. Ingersoll will coordinate efforts of the entire multidisciplinary team and ensure efficient collaboration with non-UVA personnel for the research trial. Dr. Morin are exceptionally well trained to perform their identified roles and no additional training for purposes of this project is planned.

3. How do you plan to access any study records the non-UVA personnel might maintain?

Dr. Morin will not have access to study records. No non-UVA personnel will be maintaining study records.

4. Will the non-UVA personnel be exposed to any additional risk while working on this protocol?

►NO. None of the contributors will be at risk by working on this project.

5. List name of any other institution with which they have an affiliation.

Dr. Charles Morin is a Professor of Psychology at The University of Laval in Quebec, Canada.

6. Will this person have access to subjects or data with any HIPAA identifier?

No

Dr. Morin will only have access to de-identified data.

APPENDIX: Conflict of Interest Information

1. Does anyone listed as personnel on this protocol, their spouse or any members of their immediate family serve as a director, officer, or member of an advisory board with the sponsoring company? No.

2. Does anyone listed as personnel on this protocol, their spouse or any members of their immediate family together receive direct or indirect income from cash payment, stock, stock options, own >3% equity in the sponsoring company, or have a consulting agreement etc. totaling greater than $10,000 in personal income/year (excluding salary support from study budget) from the sponsor?

No.

For more information see the UVa Conflicts of Interest Policy and FAQ at http://www.virginia.edu/vpr/objectivity.html
IF YES, has this conflict been reported?

Although personnel do not have a relationship with NIH which funds this grant, Drs. Ritterband and Thorndike have significant financial interest in a start-up company via 33 percent ownership. Via the UVA Patent Foundation, the start up company licensed the software related to development of the previous Internet intervention for insomnia in April, 2011. Under federal regulations, Drs. Ritterband and Thorndike have a financial conflict of interest (fCOI) on this study to develop and evaluate the Internet-based, behavioral interventional tool for insomnia in a clinical study.

This conflict has been reported to the Conflicts of Interest Committee. After reviewing the conflict and our proposed management plan on April 20, 2011, they unanimously resolved to adopt our proposed management plan below:

RESOLUTION IN THE CASE OF BEHEALTH SOLUTIONS, LLC AND DR. THORNDIKE AND RITTERBAND

The Conflicts of Interest Committee met on April 20, 2011 and unanimously resolved to adopt the management plan below with regard to the above referenced disclosures:

1. A faculty member without a COI will serve as the Principal Investigator of all IRB protocols that include the licensed software, under both NIH awards outlined in the disclosures. Karen Ingersoll, PhD, a tenured Associate Professor in the Department of Psychiatry and Neurobehavioral Sciences, who does not report to either Drs. Thorndike or Ritterband has agreed to serve in this role and to oversee all aspects of the clinical trials related to any of the software licensed by BeHealth Solutions. Dr. Ingersoll will make all final decisions related to conducting the trial, including data safety and monitoring procedures, as well as human subjects’ protections. In this role, Dr. Ingersoll will also supervise personnel involved in running the trial, collecting the data, and analyzing the data. Because Drs. Ritterband and Thorndike developed the computer systems being used in both clinical studies, it is possible that their expertise might be required to troubleshoot and resolve technical problems that might occur during the course of these studies; however, they will not interact with subjects or modify any study data entered into either system. Their access to raw data is limited only to the circumstance where there is a need to address the functional aspects of the programs, such as, for example, when problems arise requiring the need to debug the programs.

2. All co-investigators and study personnel will be informed of Drs. Ritterband and Thorndike’s financial relationship with BeHealth Solutions and continue to be apprised of the nature of their relationship with BeHealth Solutions. Study team members will be encouraged to report any concerns to Dr. Ingersoll that may arise due to these financial interests.

3. The IRB will also be notified of Drs. Ritterband and Thorndike’s financial interests in BeHealth Solutions and the nature of the company’s licenses to software related to that used in the specified trial and to consider appropriate language that might be included in the consent forms. Drs. Thorndike and Ritterband will not be involved in consenting subjects to participate in the study. It is recommended to the IRB that their financial interest in this research be included in the consent forms.
4. Drs. Ritterband and Thorndike will not manage or analyze any data, but they will be involved in development of resulting manuscripts. Dr. Ingersoll will co-write and approve all manuscripts related to the clinical trial to ensure the integrity of the publications derived from this research. Final decisions on the manuscripts, including any controverted points which may arise, will be made by Dr. Ingersoll.

5. Disclosure of the financial interests will be included with each publication or oral presentation.

6. Under no circumstances will publication or presentation of any research findings be constrained or delayed as a result of Drs. Ritterband and Thorndike’s financial interest in BeHealth Solutions.

7. It is possible that a trainee or trainees will participate in these clinical studies. Any participating trainees in a clinical study will report directly to Dr. Ingersoll regarding their involvement in the clinical study.

IF YES, indicate where you reported the conflict:

_XX_ Annual Reporting on Conflicts of Interest to the School of Medicine

Note: Drs. Ritterband and Thorndike have met with both Steve Wasserman and Dave Hudson. This conflict and disclosure have been reviewed by the Conflicts of Interest Committee and a management plan has been approved. See above. Grant and Contracts is also aware of this conflict.

IF NO, STOP and complete a Financial Disclosure Form which can be found at http://www.virginia.edu/vpr/objectivity/html

Before submitting your disclosure form it is recommended you contact one of the persons below to discuss this financial interest:

<table>
<thead>
<tr>
<th>School of Medicine</th>
<th>Steve Wasserman</th>
<th>243-7088</th>
</tr>
</thead>
<tbody>
<tr>
<td>School- Other</td>
<td>Dave Hudson</td>
<td>243-0900</td>
</tr>
</tbody>
</table>

If you have not previously disclosed this financial interest, additional time may be required for the Conflicts of Interest Committee and the IRB to consider your financial disclosure and protocol respectively. Consideration of significant financial interests related to research is one of the factors the IRB takes into consideration in reviewing protocol safety.

APPENDIX: Legal/Regulatory

Recruitment

The following procedures will be followed:

- Finders fees will not be paid to an individual as they are not allowed by UVa Policy
- All recruitment materials will be approved by the IRB-HSR prior to use. The advertisements will be submitted to the IRB after the protocol has been approved.
• Only those individuals listed as personnel on this protocol will recruit and or conduct the consenting process with potential subjects.

**Clinical Privileges**

The following procedures will be followed:

- Investigators who are members of the clinical staff at the University of Virginia Medical Center must have been granted clinical privileges to perform specific clinical privileges whether those procedures are experimental or standard.
- The IRB cannot grant clinical privileges.
- Performing procedures which are outside the scope of the clinical privileges that have been granted may result in denial of insurance coverage should claims of negligence or malpractice arise.
- Personnel on this protocol will have the appropriate clinical privileges in place before performing any procedures required by this protocol.
- Contact the Clinical Staff Office- 924-5871 for further information.

**Sharing of Data/Specimens**

Data and specimens collected under an IRB approved protocol are the property of the University of Virginia. You must have “permission” to share data/ specimens outside of UVa other than for a grant application and or publication. This “permission” may come in the form of a contract with the sponsor or a material transfer agreement (MTA) with others. A contract/ MTA is needed to share the data outside of UVa even if the data includes no HIPAA identifiers and no code that could link the data back to a HIPAA identifier.

- No data will be shared outside of UVa, beyond using data for a grant application and or publication, without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.
- No specimens will be shared outside of UVa without a signed contract/MTA approved by the SOM Grants and Contracts office/ OSP or written confirmation that one is not needed.

**Prisoners**

If the original protocol/ IRB application stated that no prisoners would be enrolled in this study and subsequently a subject becomes a prisoner, the study team must notify the IRB immediately. The study team and IRB will need to determine if the subject will remain in the study. If the subject will remain in the study, the protocol will have to be re-reviewed with the input of a prisoner advocate. The prisoner advocate will also have to be involved in the review of future continuations, modifications or any other reporting such as protocol violations or adverse events.

**Prisoner-** Individuals are prisoners if they are in any kind of penal institution, such as a prison, jail, or juvenile offender facility, and their ability to leave the institution is restricted. Prisoners may be convicted felons, or may be untried persons who are detained pending judicial action, for example, arraignment or trial.

For additional information see the OHRP website at [http://www.hhs.gov/ohrp/policy/populations/index.html](http://www.hhs.gov/ohrp/policy/populations/index.html)

**APPENDIX: Recruitment and Consenting**

1. **How do you plan to identify potential subjects**
_X_ Potential subject is approached by the treating physician/health care provider and given information about the study and provides the potential subject the information necessary to contact the study team if they are interested.

*Note:* Indirect contact will be the primary source of recruitment, but it is possible that when physicians learn about the study, they may elect to give their patients study-related information.

_X_ Potential subjects will not be directly identified. They will respond to an advertisement such as a flyer, brochure etc. *If this is checked #3 below should be checked INDIRECT CONTACT.*

2. **How will potential subjects be recruited?**
   - Direct contact of potential subjects by the study team via letter, phone, direct e-mail.
   - _X_ Potential subjects will be approached while at UVa Health System
   - _X_ Indirect contact (flyer, brochure, TV, broadcast emails, etc.)

3. **How will the consenting process take place?**
   Interested individuals will be directed to our study website which will provide an overview of the study, inclusion/exclusion criteria, compensation information, the informed consent, and an online interest form. Potential subject will then read and digitally sign a HIPAA Authorization Stand Alone Form. If still interested, potential participants will be prompted to complete an interest form online. The information entered on the interest form will be stored in our database on our Health Systems Computing Services (HS/CS) managed server that is configured to store data regulated by HIPAA. If an individual appears to meet criteria, s/he will be contacted by phone. While on the phone, the research coordinator will send the individual a link to his/her consent form. Individual will view consent form on his/her computer. Research coordinator will go over the entire consent form while on the phone and address any questions the person may have. Then, the individual will sign the form using his/her mouse and submit the consent form. This electronic process has already been approved by the IRB for our previous trials.

The consent form will be time and date stamped after it is submitted. The study coordinator’s signature will be electronically added. Then the signed and dated copy will be e-mailed back to the participant, and an electronic version of the consent form will also be saved in our online tracking system.

4. **Do you plan to ask the subjects to do anything for the study prior to signing a consent form?**
   - Yes. ►**IF YES, explain in detail what you will ask them to do.**
     Interested individuals will complete an interest form prior to signing consent. The interest form will ask questions regarding sleep patterns and other questions related to initial eligibility (e.g., age). The form also asks interested persons to provide contact information to allow the research coordinator to contact participants to schedule a phone interview where the consent process will occur. Prior to submitting this information, the interested candidate will read and electronically
sign a HIPAA Authorization Form indicating their consent to the “Confidentiality, Use and Disclosure of Health Information for Research Purposes” policy. Additionally, in the Consent Form, participants will be reminded that information collected via the online interest form will be used for study purposes.

5. Will the study procedures be started the same day the subject is recruited for the study?
   Yes
   The day the subject is consented, study procedures will begin (completion of phone interview),

   ► IF YES, explain in detail why the subject cannot be given more time to make a decision.
   If subject chooses to take more time to decide about participating in the study, they are welcome to do so. They are given this option.

   ► IF YES, explain in detail what will be done to assure the potential subject has enough time to make an informed decision.
   When potential participant is contacted by phone, the study is described and the consent form is explained in detail. At that time, the participant decides whether they choose to move forward and sign the consent form or whether they prefer to think further about participating. They are welcome to delay signing the consent form and re-contact the research coordinator when they feel prepared to make an informed decision.

6. Do you need to perform a “dry run” of any procedure outlined in this protocol? No.

APPENDIX: Privacy Plan for Studies With Consent

1. Describe your plan to protect the identifiable data from improper use and disclosure.
   __X__ Option # 2
   Health information may be stored with HIPAA identifiers.
   Specimens will be stored with or without HIPAA identifiers depending on security measures in place (see below).

1a. Will any of the data be stored electronically at UVa?

   ► IF YES, where will it be stored?
   __X__ an Information Technology and Communications (ITC) managed server that is configured to store data regulated by HIPAA,

1b. Will any of the data be stored in hard copy format at UVa e.g.- on paper? NO

1c. The following procedures will also be followed
   • Only investigators for this study and clinicians caring for the patient will have access to the data. They will each use a unique log-in ID and password that will keep confidential.
   • If specimens stored: The following security precautions will be implemented for specimens stored at UVa:
     • Specimens will be stored in a locked freezer/ or locked room
_X_ NA- no specimens or will not be stored at UVa

- Each investigator will sign the University’s Electronic Access Agreement available at http://www.itc.virginia.edu/policy/form/eaa.pdf and forward the signed agreement to the appropriate department as instructed on the form. _If you currently have access to clinical data it is likely that you have already signed this form. You are not required to sign it again._
- UVa Institutional Data Protection Standards will be followed http://itc.virginia.edu/security/dataprotection
- If identifiable data (_data with health information and HIPAA identifiers_) is transferred to any other location such as a desktop, laptop, memory stick, CD etc. the researcher must follow the ITC Policy “Electronic Storage of Highly Sensitive Data” http://itc.virginia.edu/security/highlysensitivedata/
- If the HIPAA identifiers and health information are combined on an additional computer off UVa premises, the researcher will follow the UVa "Guideline for Safeguards When Removing PHI Off-Premises for Work" https://www.healthsystem.virginia.edu/intranet/privacyoffice/Policies/PHI_Off_Premises.doc
  - The data will be securely removed from the server, additional computer(s), and electronic media according to the University's Electronic Data Removal Policy. https://etg07.itc.virginia.edu/policy/policydisplay?id=IRB-004
  - The data may not be analyzed for any other study without additional IRB approval

2. Describe your/central registry’s plan to destroy the HIPAA identifiers at the earliest opportunity consistent with the conduct of the research.

_ X_ The HIPAA identifiers (except full dates and or address information if needed) will be destroyed as soon as all publications are complete. _This wording would allow the researcher to keep HIPAA identifiers until all queries/ request for additional information from publisher are addressed_

3. Do you confirm that you will not reuse the identifiable data (HIPAA identifiers or health information) or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR?

This means that after the study is closed at UVa:

- _You cannot contact the subject by any method (you cannot call them, send a letter, talk to them in person about the study, etc) without additional IRB approval_
- _You cannot use the data for any research that is not already described in your IRB protocol without additional IRB approval (if you change your hypothesis you must modify your protocol)_
- _You cannot share your research data with another researcher outside of your study team without additional IRB approval_
- _Any health information with HIPAA identifiers will be shredded or discarded by using recycling bins for confidential material found in clinic settings. For large item disposal of confidential material contact Environmental Services at 2-4976 or University Recycling at 2-5050._

TABLE A: HIPAA Identifiers (Limited Data Set)
1. Name
2. Postal address information, other than town or city, state, and zip code
3. Telephone numbers
4. Fax numbers
5. Electronic mail addresses
6. Social Security number
7. Medical Record number
8. Health plan beneficiary numbers
9. Account numbers
10. Certificate/license numbers
11. Vehicle identifiers and serial numbers, including license plate numbers
12. Device identifiers and serial numbers
13. Web Universal Resource Locators (URLs)
14. Internet Protocol (IP) address numbers
15. Biometric identifiers, including finger and voice prints
16. Full face photographic images and any comparable images
17. Any other unique identifying number, characteristic, code that is derived from or related to information about the individual (e.g. initials, last 4 digits of Social Security #, mother’s maiden name, first 3 letters of last name.)

► YES, we confirm that we will not reuse the identifiable data or disclose any of this information to any other person or entity except as outlined in this protocol, except as required by law, for authorized oversight of the research study, or use it for other research unless approved by the IRB-HSR