Optimizing efficiency and impact of digital health interventions for caregivers: A mixed methods approach

National Clinical Trial (NCT) Identified Number: NCT04986904

Principal Investigator: Kelly Shaffer, PhD

Funded by: National Institutes of Health: National Center for Advancing Translational Sciences

Version Date: 16 August 2022

Key Roles and Study Governance

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PI: Heidi Donovan, PhD</td></tr>
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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Center for Advancing Clinical Translational Sciences Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training.

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

UVA Lead Principal Investigator

_____	_____	_____
Name (print)	**Signature**	**Date**

Pitt Investigator

_____	_____	_____
Name (print)	**Signature**	**Date**

ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
Pitt	University of Pittsburgh (study site)
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SHUTi	Sleep Healthy Using the Internet
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
UVA	University of Virginia (study site)

1 PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td>Title:</td><td>Optimizing efficiency and impact of digital health interventions for caregivers: A mixed methods approach</td></tr>
<tr><td>Study Description:</td><td>One hundred high-intensity caregivers with insomnia will be enrolled in this open-label pilot trial of SHUTi with pre and post-assessments. The relation of caregivers' engagement with SHUTi - and among users, the effect of SHUTi on known mechanisms of change - with caregiving-related user and environment characteristics will be tested. This single-arm design focused on intervention mechanisms (e.g., as opposed to an underpowered randomized controlled trial measuring symptom change) was chosen as it is recommended for establishing plausibility to support subsequent larger-scale efficacy testing.</td></tr>
<tr><td>Objectives & Endpoints:</td><td>
<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td>Primary</td><td></td></tr>
<tr><td>To test the association of SHUTi engagement with caregiving context.</td><td>Level of engagement: non-users (i.e., completed no Cores), incomplete users (i.e., completed 1 to 3 Cores), and complete users (i.e., completed 4 to 6 Cores)</td></tr>
<tr><td>Secondary</td><td></td></tr>
<tr><td>To describe caregivers’ barriers and motivations for SHUTi engagement</td><td>• Open-ended feedback about SHUTi
• SHUTi utility and barriers: Internet Intervention Utility, Evaluation, and Adherence questionnaires</td></tr>
<tr><td>To test the association of SHUTi efficacy on known cognitive mechanisms with caregiving context.</td><td>Cognitive mechanisms of change targeted by SHUTi
• Sleep beliefs: Dysfunctional Beliefs and Attitudes about Sleep scale
• Sleep control: Sleep Locus of Control Scale</td></tr>
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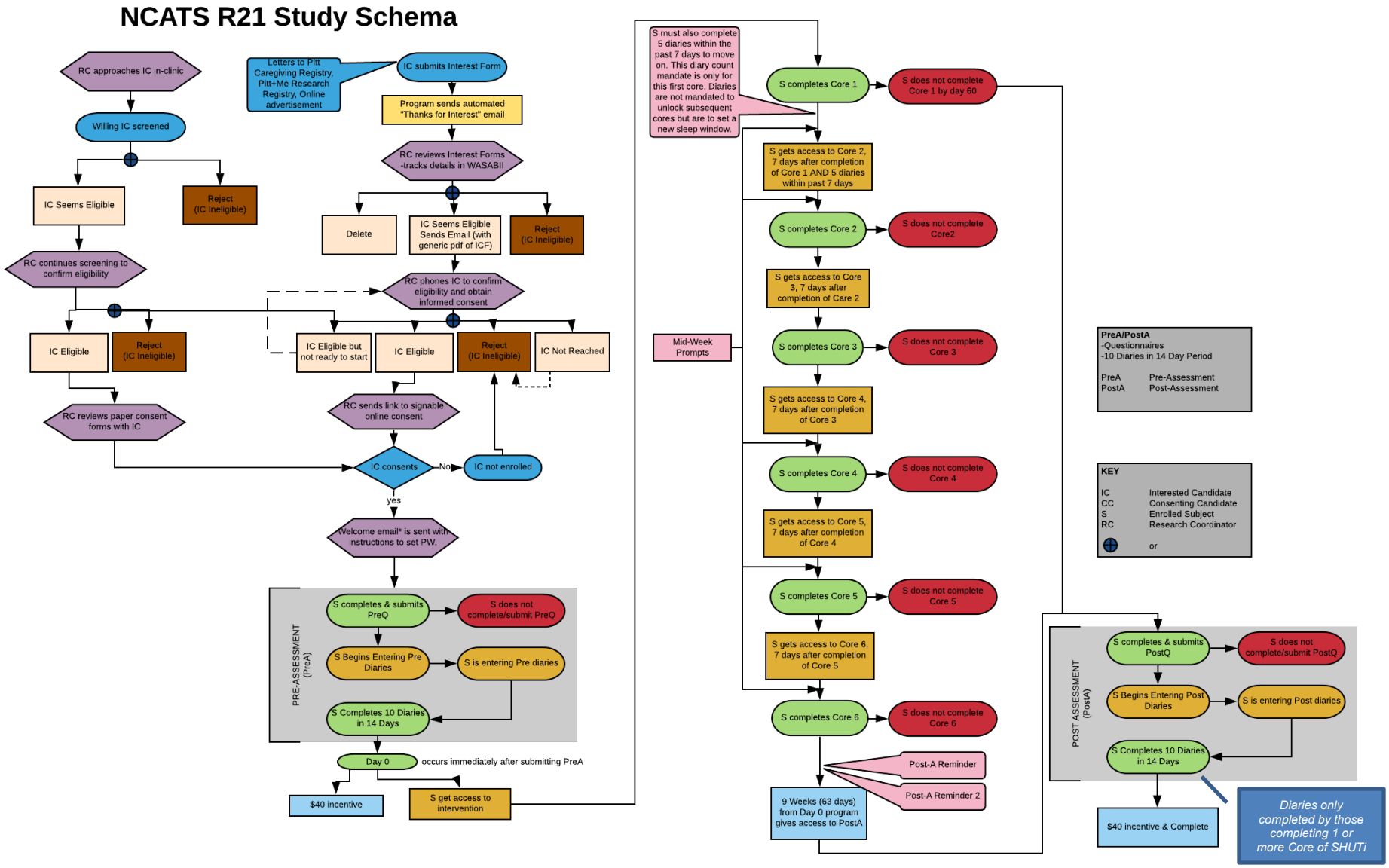
</td></tr>
<tr><td>Study Population:</td><td>Up to about 130 participants who self-report to be a caregiver with insomnia.</td></tr>
<tr><td>Description of Sites/Facilities Enrolling Participants:</td><td>This is a multi-site study enrolling participants from the University of Virginia (UVA) and the University of Pittsburgh (Pitt).</td></tr>
<tr><td>Description of Study Intervention:</td><td>Sleep Healthy Using the Internet (SHUTi) developed by Sub-I Ritterband is an NCI-designated research-tested intervention that delivers cognitive behavioral therapy for insomnia.</td></tr>
<tr><td>Study Duration:</td><td>The study will last two years.</td></tr>
</table>

Participant Duration:	Each participant will be enrolled in the study for 12 weeks.

1.2 Schema


NCATS R21 Study Schema
RC approaches IC in-clinic
Willing IC screened
IC Seems Eligible
Reject (IC Ineligible)
RC continues screening to confirm eligibility
IC Eligible
Reject (IC Ineligible)
RC reviews paper consent forms with IC
Letters to Pitt Caregiving Registry, Pitt+Me Research Registry, Online advertisement
IC submits Interest Form
Program sends automated "Thanks for Interest" email
RC reviews Interest Forms -tracks details in WASABII
Delete
IC Seems Eligible Sends Email (with generic pdf of ICF)
Reject (IC Ineligible)
RC phones IC to confirm eligibility and obtain informed consent
IC Eligible but not ready to start
IC Eligible
Reject (IC Ineligible)
IC Not Reached
RC sends link to signable online consent
IC consents
No
IC not enrolled
yes
Welcome email* is sent with instructions to set PW.
PRE-ASSESSMENT (PreA)
S completes & submits PreQ
S does not complete/submit PreQ
S Begins Entering Pre Diaries
S is entering Pre diaries
S Completes 10 Diaries in 14 Days
Day 0
occurs immediately after submitting PreA
$40 incentive
S get access to intervention
S must also complete 5 diaries within the past 7 days to move on. This diary count mandate is only for this first core. Diaries are not mandated to unlock subsequent cores but are to set a new sleep window.
Mid-Week Prompts
S completes Core 1
S does not complete Core 1 by day 60
S gets access to Core 2, 7 days after completion of Core 1 AND 5 diaries within past 7 days
S completes Core 2
S does not complete Core2
S gets access to Core 3, 7 days after completion of Care 2
S completes Core 3
S does not complete Core 3
S gets access to Core 4, 7 days after completion of Core 3
S completes Core 4
S does not complete Core 4
S gets access to Core 5, 7 days after completion of Core 4
S completes Core 5
S does not complete Core 5
S gets access to Core 6, 7 days after completion of Core 5
S completes Core 6
S does not complete Core 6
Post-A Reminder
Post-A Reminder 2
9 Weeks (63 days) from Day 0 program gives access to PostA
POST ASSESSMENT (PostA)
S completes & submits PostQ
S does not complete/submit PostQ
S Begins Entering Post Diaries
S is entering Post diaries
S Completes 10 Diaries in 14 Days
$40 incentive & Complete
PreA/PostA
-Questionnaires
-10 Diaries in 14 Day Period
PreA Pre-Assessment
PostA Post-Assessment
KEY
IC Interested Candidate
CC Consenting Candidate
S Enrolled Subject
RC Research Coordinator
or
Diaries only completed by those completing 1 or more Core of SHUTi

2 INTRODUCTION

2.1 Study Rationale

One in six American adults provide care for a loved one with disabling illness, and these family caregivers are more likely to experience insomnia and other psychological concerns than the general population. Multiple existing, evidence-based digital health interventions may effectively address caregivers' psychosocial needs and increase caregivers' access to supportive care. For example, Sleep Healthy Using the Internet (SHUTi) developed by Dr. Ritterband is an NCI-designated research-tested intervention that delivers cognitive behavioral therapy for insomnia. A key translational research question remains about existing evidence-based digital health interventions like SHUTi, namely, what level of tailoring would be necessary and sufficient achieve optimal engagement with and efficacy of these interventions for caregivers? To address this research question, up to about 130 high-intensity caregivers with insomnia will be recruited to complete a baseline assessment of insomnia and caregiving context. Caregivers will then receive access to SHUTi in an open-label trial, then complete post assessments. Participants will be categorized according to their level of engagement with the 6 intervention "Cores": nonusers (i.e., completed no Cores), incomplete users (i.e., 1 to 3 Cores), and complete users (i.e., 4 to 6 Cores). SHUTi engagement will be measured with caregiving context. First, we will test whether caregivers' engagement with SHUTi (i.e., being a non-user vs. incomplete user vs. complete user) is associated with their user characteristics (i.e., caregiving strain, self-efficacy, and guilt) and environment characteristics (i.e., proximity to care recipient; care recipient functional, cognitive, and behavioral status; caregiving tasks). Second, we will describe caregivers' barriers to and motivations for SHUTi engagement from their responses to open-ended surveys, and how caregiver-specific tailoring may improve uptake and usage. Thematic coding will also examine how caregivers' recommendations generalize to other evidence-based digital health interventions, and findings will be validated using synthesized member checking.

The effects of SHUTi will be evaluated on known cognitive mechanisms of change targeted by SHUTi (i.e., more adaptive sleep beliefs, internalized sleep locus of control) are associated with differences in caregiving-related user and environment characteristics. These findings are not only necessary to direct next research on tailoring and testing SHUTi for caregivers specifically, but also to advance the science towards our long-term goal, namely, to improve the quality and impact of digital health interventions for caregivers, while reducing intervention development inefficiency – a goal identified as a high priority for current caregiving research. As such, findings will be translatable across research-tested intervention programs and hold significant promise to reduce inefficiencies in developing digital health interventions for caregivers, while also increasing intervention impact and reach for this underserved population.

2.2 Background

An estimated 47.9 million Americans provide informal, unpaid care to one or more adult family members with serious health conditions. [2] About 40% of these caregivers are in high-intensity caregiving situations, meaning they spend a significant amount of time caregiving (49 hours/week on average) and assist with multiple care tasks (3 activities of daily living [ADL] and 5 instrumental ADL [IADL] on average). Compared to lower-intensity caregivers, high-intensity caregivers have more difficulty accessing affordable support services, although they are also more interested in support to manage their own

emotional and physical well-being.[2,3] Support from family members to seriously ill individuals is critical to the sustainability of the U.S. healthcare system, [14] but it places a significant strain on these caregivers. Insomnia is among the most common, distressing, and impairing psycho-physiological issue for caregivers, who report this problem more commonly than non-caregivers.[15,16] Compared to about 33-50% in the general population,[17] up to 90% of caregivers report sleep impairment,18 although rates have varied by contexts – for example, 27% in Parkinson's caregivers,19 50-75% in cancer,[20–22] and 63-68% in dementia.[18,23,24] Sleep impairment contributes to caregivers' anxiety, depression, and physical morbidity,[21,25–29] which affect caregivers more severely than those in the general population.[30–33] Moreover, caregivers' poor sleep also ultimately affects their care recipients. Because it increases their distress, sleep-deprived caregivers are more likely to exhibit harmful caregiving behavior[34] and less able to meet the practical and social-emotional needs of the care recipient. [35,36] Additionally, care recipients' sleep disturbance is interrelated with their caregivers'.[37,38] Accessible and effective insomnia interventions for caregivers are therefore important to the well-being of both caregivers and care recipients. Although such interventions are effective, they suffer from low enrollment, high dropout, and limited reach to caregivers who already have inadequate healthcare access, like caregivers from lower SES or those in rural areas. [39–43] Digital health interventions can lower barriers to entry to supportive care for caregivers as they are conveniently accessible anywhere and anytime from an Internet-enabled device. Indeed, caregivers express strong interest in Internet interventions because of their convenience.[44–46] Multiple existing, efficacious digital health interventions may effectively address caregivers' psychosocial needs. For example, Sleep Healthy Using the Internet (SHUTi), developed by Dr. Ritterband, is an NCI designated research-tested intervention that delivers cognitive-behavioral therapy for insomnia (CBT-I).[47,48] Most digital health interventions tested among caregivers, however, have been developed de novo for specific caregiving contexts.[49–54] Tailoring interventions in this way is rooted in behavior change theory: tailoring to a user's characteristics increases information salience, which increases a user's attention to information, which ultimately increases the likelihood that the information will motivate behavior change.[8] When tested empirically, tailoring typically adds only small gains in outcomes relative to generic materials, although gains are typically maintained over time.[10,55,56] The decision to tailor, and how to tailor, must balance expected benefits of increased specificity against reduced reach and increased costs (time and financial). The implicit assumption underlying existing research – where de novo interventions are developed for caregivers – is that caregivers have different deficits, risk factors, and needs from non-caregivers. There is reason to believe this is true and that caregiving has unique psychological and environmental factors that would affect use and impact of insomnia interventions specifically, and digital health interventions broadly. Specific to insomnia interventions, caregivers' insomnia can be perpetuated by worry about the negative impact of sleep loss on their ability to meet the demands of caregiving and a feeling of helplessness to improve their sleep due to their caregiving responsibilities.[22,28,57] Indeed, caregivers do frequently need to organize their sleep around the needs of the care recipient[38] and often need to support the care recipient at night with symptom management or nighttime behavioral issues.[22,28] When considering digital health interventions more broadly, research repeatedly highlights primary barriers to caregivers' help-seeking being their self-sacrifice – the de-prioritization of caregivers' own needs behind the needs of the care recipient, particularly prominent among high-intensity caregivers – and caregivers' guilt when they do prioritize their needs. [58–61] Caregivers' often busy and chaotic schedules – also particularly true of high-intensity caregivers – likewise commonly get in the way of their ability to commit to consistently

participating in interventions. [59,61] Although these factors lend plausibility to the assumption that tailoring insomnia and digital health interventions for caregivers is needed, this assumption has not often been tested, and therefore the extent to which caregivers want and need tailoring for interventions is not known. This assumption may be comprehensively examined through the Model for Internet Interventions, [1] published by our team as the first testable theoretical model that guides digital health intervention development and evaluation by conceptualizing the processes that determine symptom improvement through the use of such interventions.

2.2.1 Relevant Clinical Experience

The SHUTi intervention was developed and refined through the Model for Internet Interventions.[1] The website (6 Cores of CBT-I content tailored to users) and support (automated email reminders to complete diaries and Cores) are established. A relatively consistent pattern in SHUTi use, or engagement, has emerged across completed trials: About 90% of participants complete at least Core 1 and 65% of participants complete at least Core 4 or more of the program.[5,7,75,76] Those completing through at least Core 4 are considered “completers” as they have completed content related to primary change mechanisms; also, almost all (>90%) continue on to complete all 6 Cores. One trial of SHUTi among people with comorbid insomnia and depression found that only 40% completed all 6 Cores;[6] this lower rate is not surprising given engagement is affected by depressive symptoms.[77] Engagement is important, given that trials have also established that the more participants use SHUTi, the more they benefit.[5,7] SHUTi treatment gains have been demonstrated to be mediated through changes to cognitive mechanisms (i.e., more adaptive sleep beliefs and internalized sleep locus of control).[78] Across trials, which have included medically and psychiatrically diverse participants, SHUTi shows statistically and clinically significant reductions in participants’ insomnia symptom severity (ds = 1.17-2.34).[4–7,75,76,79,80] Therefore, because the support and website variables will be held constant (i.e., SHUTi), we can isolate the effects of user characteristics and environment related to the caregiving context. Our most recent trial of SHUTi (NCT03213132, targeting older adults with insomnia, completed September 2020) assessed whether individuals were caregivers. Of 207 participants randomized to SHUTi, 18 self-reported as a caregiver (9%, of whom n = 7 [39%] lived with the care recipient). Compared to non-caregivers, caregivers reported less improvement in their insomnia after using SHUTi (ISI score difference = 2.37 [95% CI = 0.17, 4.57], p = .03). Caregivers also reported less impact of SHUTi on their sleep quality compared to noncaregivers ($\chi 2$ [1, N = 190] = 4.78, p = .03). There were no significant differences (ps > .10) between caregivers’ and non-caregivers’ change in cognitive mechanisms, although CIs suggested less benefit for caregivers. The amount that caregivers logged into SHUTi (M = 80.56 logins) also did not differ significantly from non-caregivers (M = 92.92 logins; t[22.83] = 1.10, p = .28 [diff 95% CI = -10.91, 35.64]; Shaffer, Camacho, Mattos, Buysse, Donovan, Ingersoll, & Ritterband, under review). These preliminary data support the capability of caregivers to engage with SHUTi, yet suggest caregivers experience less benefit from the intervention relative to noncaregivers. These data are limited, however, given the small sample and minimal information known about this caregiver sample, as caregiving was not a focus of this trial. Our proposed study is therefore necessary to better understand how caregiving context impacts SHUTi use and mechanisms, which ultimately drive symptom improvement, in order to understand how SHUTi may need to be optimized for caregivers. Summary of preliminary research: Taken together, data demonstrate: (1) caregivers are interested in CBT-I and digital health interventions, yet tailoring may be needed to optimize their outcomes, (2) SHUTi

is a vetted Internet-based treatment for insomnia, and (3) our combined experience to support our successful completion of this study, which builds logically from our past research to address our central question of: What tailoring is necessary and sufficient to achieve optimal engagement with and efficacy of SHUTi for caregivers?

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

There always exists the potential for loss of private information. Participating caregivers risk potential loss of confidentiality of their self-reported demographics, measures of caregiving context and insomnia symptoms and mechanisms, and contact information. Participants will need to give study personnel their email address to which electronic questionnaires and reimbursement can be sent.

Participants will be asked questions of a sensitive or personal nature (e.g., care recipient's condition, psychological functioning), which potentially could cause some discomfort or embarrassment in answering these types of questions.

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.

Among those who choose to use SHUTi, in following some intervention recommendations, participants may be asked to restrict sleep at certain times, which could lead them to initially feel more tired. This increase in tiredness could potentially exacerbate cancer-related fatigue that some participants may be experiencing.

All participants will be able to access support for technical difficulties. However, no human therapy support will be provided. Removing human therapy support from provision of care can vastly increase the ability to widely disseminate treatment, but it may be associated with several risks. Internet-delivered programs are more restricted with respect to the tailoring of intervention recommendations. For example, the Internet intervention tailors which cognitive strategies are recommended based on users' endorsement of distorted cognitions, but will not be able to make the recommendation to skip the Cognitive Core altogether. With a clinician, treatment can potentially be more tailored (e.g., make the decision that a particular patient does not need to focus on the cognitive strategies at all).

There may be a risk that participants who have suicidal ideation will not be appropriately managed given the geographic limitations of conducting a study remotely.

2.3.2 Known Potential Benefits

Participants may learn information about the diagnosis of insomnia, its etiology, general treatment strategies, methods of regular monitoring, and prognosis.

Participants could potentially benefit from having improved sleep, improved health, reduced psychological distress, and improved quality of life. The potential benefits to the caregiving community are that this intervention, and possible future digital health interventions like it, would allow for a greater number of caregivers to have access to a low-cost and empirically-validated treatment for insomnia. It could potentially reduce health disparity by providing treatment that has not previously been available to

caregivers in more remote areas where access to a behavioral medicine sleep specialist is limited.

2.3.3 Assessment of Potential Risks and Benefits

The risk of discomfort in answering personal questions, potential for loss of privacy, and risk of increased sleepiness during sleep restriction in the SHUTi program is balanced against the potential to achieve optimal engagement with and efficacy of an evidence-based treatment for insomnia among caregivers, which would be the first treatment of its kind tested among this population. The risk/benefit ratio seems reasonable given that there is a chance of long-term benefit to delivering more accessible, effective interventions to caregivers with minimal chance of harm to study participants.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To test the association of SHUTi engagement with caregiving context.	Level of engagement: non-users (i.e., completed no Cores), incomplete users (i.e., completed 1 to 3 Cores), and complete users (i.e., completed 4 to 6 Cores)
Secondary	
To describe caregivers' barriers and motivations for SHUTi engagement	• Open-ended feedback about SHUTi • SHUTi utility and barriers: Internet Intervention Utility, Evaluation, and Adherence questionnaires
To test the association of SHUTi efficacy on known cognitive mechanisms with caregiving context.	Cognitive mechanisms of change targeted by SHUTi • Sleep beliefs: Dysfunctional Beliefs and Attitudes about Sleep scale • Sleep control: Sleep Locus of Control Scale

4 STUDY DESIGN

4.1 Overall Design

This study comprises a single-arm (nonrandomized) clinical trial with quantitative and qualitative data collection.

4.2 End of Study Definition

Primary completion date is the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes defined as the final date for the collection of data for the primary endpoint.

Study completion date is the date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated.

5 STUDY POPULATION

In order to verify the age and identity of participants, individuals' information provided on the online interest/prescreening form may be confirmed through Transunion, an online people search vendor. When indicated (e.g., not referred from a research registry), the study coordinator will enter and/or review the individual's name (first and last), year of birth, phone number, and email to confirm the individual's age and identity. Individuals who do not match on entered information will be emailed to inform them they do not qualify for the study. Individuals whose match remains unclear will be contacted to confirm their information in case they made an error in completing the interest form.

5.1 Inclusion Criteria

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

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged ≥ 18 years of age.
4. Able to speak and read English.
5. Self-report providing high-intensity unpaid care (e.g., practical, medical, and/or emotional support) to a family member or "family-like" close individual, operationalized as a function of time spent caregiving and care task involvement.
6. Self-report expecting to continue provide high-intensity care for at least another 3 months.
7. Have access to any Internet-enabled device (computer, tablet, smartphone) and willing to be emailed about the study.
8. Insomnia severity index score $\geq$ 10
9. Residing in the United States or U.S. territory

5.2 Exclusion Criteria

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

Exclusion Criteria:

1. Unusual average bed/wake times, including for shift work
2. Current behavioral/psych treatment for insomnia
3. Medical contraindication (RLS/PLMD, OSA, narcolepsy, parasomnia, dementia, Parkinson's, Huntington's, stroke, TBI, brain infection/tumor, pregnancy/breastfeeding, hyperthyroidism, cancer, severe respiratory disease, epilepsy)
4. Psychiatric contraindications (mania/hypomania, alcohol or substance abuse/dependence)
5. Changes to prescription medications in the past 3 months (sleep, steroid, amphetamine, other wake-promoting)
6. Severe computer literacy challenges

5.3 Justification for Study Population

In selecting participants for this project, due notice is taken of the National Institutes of Health policy concerning inclusion of women and minorities in clinical research. The proposed study will be open to men and women of all ethnic and racial backgrounds. We will not exclude participants based on their race, ethnicity, or gender. In 2020, the National Alliance for Caregiving (NAC), in collaboration with AARP, published their executive summary based on data collected from 1,392 caregivers.[2] Weighted by population estimates, it is estimated that caregivers are predominantly (61%) female, a gender distribution that is in accord with the majority of studies of cancer caregivers. Therefore, we expect an equivalent proportion of our participants (61%) will be women. This expectation is also supported by the fact that insomnia is approximately twice as prevalent among women compared to men.[104]

Every effort will be made to recruit minoritized populations and ensure no selection bias, beyond the need to speak English. To estimate the racial distribution of caregivers who might be reached through in-clinic recruitment at UVA, given our catchment area spanning counties in both Virginia and West Virginia, there are demographic data from 13,137 patients receiving a diagnosis with any malignant neoplasm at the UVA Cancer Center in 2019. Of the over 13,800 patients with a cancer diagnosis to receive oncologic care at UVA in 2019, 75% are non-Hispanic White, 13% are African American, 4% are Hispanic, and 1% are Asian (7% unknown). Of the over 1,100 patients with a dementia-related diagnosis who received care at UVA Memory and Aging Care Clinic in the past year, 78% are non-Hispanic White, 14% are African American, 2% are Hispanic, and 1% are Asian (5% unknown). We will also recruit participants via the University of Pittsburgh Caregiver Research Registry and the Clinical Translational Science Institute (CTSI) Pitt+Me Research Participant Registry. The Caregiver Research Registry, part of the Pitt Center for Social & Urban Research Survey Research Program, comprises over 1,000 self-identified caregivers who are representative of the Western Pennsylvania population and are willing to participate in research studies. Pitt+Me is an institutional research participant registry with the primary objective of identifying and recruiting UPMC patients of all ages from every University of Pittsburgh Medical Center point-of-

service location (5.5 million outpatient visits and 388,000 inpatient admissions and observation cases annually), as well as community member volunteers, who may be eligible to participate in ongoing Pitt clinical research studies. To date, over 230,000 participants have enrolled in the Pitt+Me registry. The Pitt CTSI Integrating Special Populations Core, which comprises special population liaisons who have unique expertise in engaging underrepresented populations in research, in order to support recruitment of racial and ethnic minority caregivers to this study. With these resources and supported by additional community outreach support from the University of Virginia integrated Translational Health Research Institute of Virginia (iTHRIV) and the Pitt CTSI, we will aim for a sample racial distribution in proportion to that reported from the 2020 NAC study, which estimated that caregivers in the U.S. are 61% Non-Hispanic White, 14% African American / Black, 17% Hispanic / Latinx, and 5% Asian American, and 3% other race or multiracial.[2]

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (for NIH studies) and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.5 Strategies for Recruitment and Retention

For clinic-based recruitment, caregivers will be introduced to the study in one of two primary ways: 1) in person, while attending a clinic appointment with an adult patient or 2) study flyers posted in the clinic rooms. Trained research assistants at both UVA and Pitt will be available to meet potential participants in-clinic or discuss the study by phone, and the study team members also have robust connections with clinic staff to support participant recruitment as well.

For recruitment via participant registry outreach, caregivers will be introduced to the study in one of three primary ways: 1) by telephone outreach, 2) by email and/or letter outreach, or 3) by matching with our study via the Pitt+Me research study database. The Caregiver Research Registry, part of the Pitt Center for Social & Urban Research Survey Research Program, comprises over 1,000 self-identified caregivers who are representative of the Western Pennsylvania population and are willing to participate in research studies. We will also reach out to care partners who have indicated willingness to be contacted in research studies via the Pitt Alzheimer's Disease Research Center (ADRC). We will also recruit individuals enrolled in the *Contact Database for UVA Cancer Center Catchment Area Survey Participants (UVA IRB-SBS 3993).* This contact database includes participants who opted into being recontacted about future studies when they completed the UVA Cancer Center catchment area survey (as has been approved by UVA IRB-HSR previously, see HSR 22747 exempt protocol as example).

We will also utilize online advertisement and promotion methods to distribute information about our study. This may include posts and/or advertisements through Facebook, Instagram, Reddit, Twitter, and other websites pertinent to family caregiving and digital

health research. Study information may also be distributed through pertinent listservs and newsletters by community and partner organizations. Potentially interested individuals will be directed to our study website and provided with contact information for study staff.

6 STUDY INTERVENTION

6.1 Description of Study Intervention(s)

Type	Name	Investigational or Standard of Care (SOC)	Description
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Sleep Healthy Using the Internet (SHUTi)	Interventional	SHUTi is a self-guided, interactive, and tailored Internet-based Program that incorporates the primary tenets of face-to-face cognitive behavioral therapy (CBT) for insomnia. Content is presented in six Cores, with a new Core available seven days after completion of the previous Core. SHUTi relies on user-entered sleep diaries to track progress and Tailor recommendations. Each Core parallels the structure of traditional Weekly face-to-face CBT-I sessions and includes: 1) examination of Core objectives, 2) review and feedback on homework and sleep diary from the prior week, 3) teaching new intervention material, and 4) assignment of homework. Intervention content is enhanced through goal-setting, graphical feedback based on the participant's symptoms, animations and illustrations to enrich comprehension, quizzes to test and enhance user knowledge, vignettes to promote identification with material, and video-based expert explanations.

6.2 Registration, Randomization and Blinding

All participants must sign the consent form prior to determination of eligibility for this study. This study does not involve any blinding or masking procedures. Subjects will be told which treatment they are receiving.

7 STUDY CLOSURE, STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to sponsor. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the Institutional Review Board (IRB) and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility
- Change in funding status

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, Data and Safety Monitoring Committee (if applicable) and/or Food and Drug Administration (FDA) (if applicable).

Participants receiving study treatment at the time of study discontinuation should complete procedures described in *section* 7.4.

7.2 Participant Discontinuation/Withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

A participant's study treatment would be discontinued for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant (see *section 7.3* for dose-limiting toxicities)
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study intervention.
- Participant decision to withdraw from study treatment and/or the study
- Initiation of prohibited intervention or medication

The reason for participant discontinuation or withdrawal from study treatment will be recorded. Participants who sign the informed consent form but do not receive the

study intervention may be replaced. Participants who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced. Participants that withdraw from the study (not only from study treatment, but all study follow-up) will not be contacted for any further study visits.

A participant will be considered lost to follow-up if he or she fails to complete pre-assessment and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to complete assessments:

- The site will attempt to contact the participant and counsel the participant on the importance of maintaining the program and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant.
- These contact attempts should be documented in the study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Study Materials and Methods

Participating caregivers will be instructed on how to complete the pre-assessment battery of online questionnaires using either computer or mobile device as the participant prefers. Estimated completion times are 30 minutes for questionnaires. Upon completing questionnaires, participants will complete 10 daily sleep diaries within 14 days. Participants will be compensated $40 upon pre-assessment completion.

After participants complete pre-assessment, they will receive access to SHUTi. Participants will be emailed a unique username and password in order to log on and securely access SHUTi for 9 weeks. The intervention can be accessed via an Internet enabled device, including a computer, tablet, or smartphone. At the start of week ten, regardless of intervention progress, participants will be instructed to complete their online post assessment.

Non-users' (i.e., those who completed 0 SHUTi Cores) post-assessment will include an open-ended survey regarding barriers to SHUTi adoption, the extent to which barriers were related to caregiving, and what modifications may have increased their motivation to try SHUTi. Users' (i.e., those who completed 1 or more SHUTi Cores) post-assessment will include an open-ended survey assessing SHUTi usage barriers and motivations, the extent to which these were related to caregiving, and how tailoring may improve usage by increasing salience to caregivers. SHUTi users will also complete 10 daily sleep diaries in 14 days as part of post-assesement. Participants will be compensated $40 upon post-assessment completion.

Caregivers who agree to be contacted for follow-up will be returned a concise report of results from the analyses as part of synthesized member checking procedures, where caregivers will be asked to review the report and comment on how results compare/contrast with their experiences and needs.

Sources of research materials:
The sources of research material will include:
(1) self-report questionnaires completed over the Internet (including caregiving-related user- and environment characteristics; as well as demographics, sleep, self-efficacy and other health/psychosocial constructs);
(2) telephone interview to inquire about sleep problems, insomnia treatment history, and computer/Internet usage;
(3) daily symptom diaries collected over the Internet to track sleep symptoms (e.g., minutes to fall asleep) in order to automatically tailor treatment recommendations; and
(4) open-ended survey items related to either barriers to SHUTi adoption, the extent to which barriers were related to caregiving, and what modifications may have increased their motivation to try SHUTi (non-users) or SHUTi usage barriers and motivations, the extent to which these were related to caregiving, and how tailoring may improve usage by increasing salience to caregivers (users).

All data will be collected explicitly and exclusively for this study and will be maintained following HIPAA regulations. Data collected through the internet will be obtained through secured means and stored on our private servers. Personal Health Information (PHI) will be stored separately from study data on a different HIPAA compliant server. Only study staff with the requisite IRB-approved Human Subjects Training will have access to participant data.

Surveys will be performed according to the Table below:

		Time Point	
Variable / Measure	Outcome measured	Pre	Post
Screening			
Caregiving	High-intensity caregiving (based on National Alliance of Caregiving intensity index), future duration	*Screen*	
Internet access	Regular Internet and email access	*Screen*	
Contact / verification	Age/year of birth, name, zip, phone, email	*Screen*	
Insomnia	Insomnia Severity Index	*Screen*	
Sleep	Usual bed/wake times (phase shift), shift work, current psychological/behavioral treatment for insomnia	*Screen*	
Medical contraindications	Dx'ed with: RLS/PLMD, OSA, narcolepsy, parasomnia, dementia, Alzheimer's, Parkinson's, Huntington's Symptoms of: RLS, OSA Ever/recovered: Stroke, TBI, Brain infection, brain tumor Current: pregnancy/breastfeeding, hyperthyroidism, cancer, respiratory disease Current/managed: Epilepsy Current/3-mo stable: Steroids, amphetamines, stimulants, prescribed sleep medications	*Screen*	
Psychological/ Psychiatric Contraindications	MINI: Mania/hypomania, Alcohol dependence/abuse, Substance dependence/abuse Dx'ed with psychosis or schizophrenia	*Screen*	
Covariates			
Sociodemographics	Age, household income, health literacy,	✓	

Health-related Quality of Life	PROMIS: 2-item Global Physical Health	✓	✓
General Distress	Patient Health Questionnaire-4	✓	✓
Predictors: Caregiving-related user characteristics			
Caregiving strain	Pearlin Stress Scale – Caregiving Overload subscale	✓	✓
Caregiving self-efficacy	Pearlin Stress Scale – Caregiving Competence subscale	✓	
Caregiving guilt	Caregiver Guilt Questionnaire – Guilt about doing wrong by the care recipient, guilt about not rising to the occasion as a caregiver, guilt about self-care subscales	✓	
Predictors: Caregiving-related environment characteristics			
Proximity to CR	Whether bedpartner, live together but not bedpartner, other situation	✓	
CR functional status	Modified Barthel Activities of Daily Living [ADL] Index	✓	
CR cognitive status	Pearlin Stress Scale – Cognitive Status subscale	✓	
CR problem behavior	Pearlin Stress Scale – Problematic Behavior subscale (includes night-time problems)	✓	
Caregiving tasks	Involvement in supporting ADL, Instrumental ADL, and nursing tasks	✓	
Changes in caregiving	Single item question (with follow-up open-ended response) if caregiving situation has significantly changed during study		✓
Aim 1 Outcomes: SHUTi engagement (Core completion recorded through SHUTi online platform)			
Core completion	Non-user (no Cores completed); Incomplete user (1-3 Cores); Complete user (4-6 Cores)	*Through SHUTi*	
Open-ended feedback	Free-response survey items – separate surveys for non-users and users		✓
SHUTi utility and barriers	Internet Intervention Utility, Evaluation, and Adherence Questionnaires – select items		✓*
Aim 2 Outcomes: SHUTi efficacy on known cognitive mechanisms			
Sleep beliefs	Dysfunctional Beliefs and Attitudes About Sleep	✓	✓*
Sleep control	Sleep Locus of Control Scale	✓	✓*
Exploratory: Preliminary Efficacy			
Insomnia severity	Insomnia severity index	✓	✓
Sleep diary metrics	10 days of sleep diaries in 14 day period	✓	✓*

**SHUTi users only*

8.1.1 Assessment of Adverse Events

The PI (Dr. Shaffer) is primarily responsible for the reporting of adverse events; all members of the research staff are responsible for the assessment of adverse events. All spontaneous reports by participants, observations by research staff, reports to research staff by family or medical care providers, etc., will be investigated. The investigators will assess the relationship of the adverse event as not related, unlikely to be related, possibly related, probably related, or definitely related using standard criteria for clinical trials.

9 DATA AND SAFETY MONITORING PLAN

9.1 Adverse Events and Serious Adverse Events

9.1.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

9.1.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.1.3 Classification of an Adverse Event

9.1.3.1 Severity of Event

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

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

9.1.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease, other drugs or chemicals, or other interventions.

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

9.1.3.3 Expectedness

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected by assessing all AEs against cumulative study intervention experience. Expectedness for adverse events and expectedness for the purposes of expedited reporting will be determined based on review of the following reference documents that describe the nature, severity, and frequency of the events.

9.1.4 Time Period and Frequency for Event Assessment and Follow-Up

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

All AEs related, probably related or possibly related to the study intervention including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. AEs that are deemed related, probably related or possibly related to the study intervention that occur while on study must be documented appropriately. AEs will be followed to adequate resolution.

Any medical condition (including a laboratory abnormality) that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's baseline medical condition worsens at any time during the study and the change is deemed related, probably related or possibly related to the study intervention, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Clinical Coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study intervention. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9.1.5 Adverse Event Reporting

Add adverse events will be reported to the University of Virginia IRB-HSR according to guidelines. Any unanticipated problem or serious and unexpected adverse events will require re-evaluation of the risk of the study. Dr. Shaffer will be the person to whom all unanticipated problems or serious and unexpected adverse events, whether psychological or medical, are initially reported. Dr. Shaffer is a licensed clinical psychologist who can evaluate whether the events are SAEs or AEs. Dr. Shaffer will be responsible for ensuring that all unanticipated problems or serious and unexpected adverse events are reported within 48 hours to the IRB and NCATS. Adverse events will be monitored carefully and any necessary steps will be taken to maintain participant safety. Any change to the procedures will be forwarded to the IRB for approval. The NCATS Project Officer will receive an annual report summarizing all adverse events.

9.2 Protocol Deviation

9.2.1 Definition of Protocol Deviation

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

9.2.2 Reporting of a Protocol Deviation

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported to Dr. Shaffer.

9.3 Participant Withdrawals/Dropouts Prior to Study Completion

Participants who withdraw consent and those dropping out of the study secondary to an AE will be reported to the IRB of record according to IRB guidelines.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

Primary hypothesis: caregivers' engagement with SHUTi (i.e., being a non-user vs. incomplete user vs. complete user) will be associated with their caregiving-related user characteristics (i.e., caregiving strain, self-efficacy, and guilt) and environment characteristics (i.e., proximity to care recipient; care recipient functional, cognitive, and behavioral status; caregiving tasks).

Secondary hypothesis: the effects of SHUTi on cognitive mechanisms of change targeted by SHUTi (i.e., more adaptive sleep beliefs, internalized sleep locus of control) will differ by caregiving-related user characteristics (i.e., caregiving strain, self-efficacy, and guilt) and environment characteristics (i.e., proximity to care recipient; care recipient functional, cognitive, and behavioral status; caregiving tasks).

10.2 Sample Size Determination

We will enroll up to about 130 high-intensity caregivers with insomnia into this single-arm (nonrandomized) trial. The minimum sample size to achieve is 100. Based on completion rates from Dr. Donovan's (University of Pittsburgh site PI) untailored Internet depression management program (non-users = 35%; incomplete = 40%; complete = 25%) and averages across SHUTi trials (non-users = 10%; incomplete = 25%; complete = 65%), we estimate that the sample in the proposed trial will break down as follows: 22% non-users, 33% incomplete users, 45% complete users. Assuming these response rates, the minimally detectable proportional odds (minOR) analyses at power = 80% with α = .05 would be a moderate effect size[94] (minOR= 2.9) for a sample size of N = 100 based on rate of dichotomized predictor exposures (computed using the Whitehead formula[95] in R Hmisc[96]; see Table below). Controlling for baseline values of cognitive mechanisms and covariates, an expected sample size of 78 users (33 incomplete + 45 complete) would have 80% power with α = .05 to detect a small effect size of a user or environment characteristic on cognitive mechanisms at post (R_2 = .04 < .10).

	Caregiving Strain		
N=100	Above *Mdn*	Below *Mdn*	% sample
Non-user	16	6	22%
User	34	44	78%
% sample	50%	50%	OR=3.4

10.3 Statistical Analyses

10.3.1 Analysis of the Primary Efficacy Endpoint(s)

To test whether SHUTi engagement is associated with caregiving context, ordered logistic regressions assuming proportional odds will be fit for each caregiving-related user and environmental characteristic on SHUTi core completion, a 3-level ordinal

dependent variable (i.e., non-user vs. incomplete user vs. complete user). Models will control for a pre-specified set of covariates (i.e., age, household income, health literacy, mental and physical health related quality of life) that are not specific to caregivers, but affect both caregiving context factors [35,72] and digital health engagement.[77,87] Where the proportional odds assumption is violated ($p < .05$), follow-up sensitivity analyses will be conducted: two logistic regressions comparing proportional odds between non-users vs. users (incomplete and complete) and between non-completers (non-users and incomplete users) vs. complete users. Secondarily, we will assess whether caregiving-related user and environmental characteristics change during the course of the intervention period and test whether this change is related to engagement using a structural equation mediation modeling approach.[88] For users, we will also examine the associations between user and environment characteristics with SHUTi evaluations on the Internet Intervention Utility, Evaluation, and Adherence Questionnaires.

10.3.2 Analysis of the Secondary Endpoint(s)

To describe caregivers' barriers and motivations for SHUTi engagement, qualitative coding of users' open-ended survey responses from post-assessment will be conducted via Dedoose software. Data will be coded using two methods: First, using an a priori codebook to tag data according to whether it is: (a) specific to SHUTi; (b) specific to CBT-I, but not exclusively SHUTi; or (c) specific to digital health interventions, but not exclusively SHUTi. This will facilitate examination of the extent to which caregiver-specific tailoring recommendations are specific to SHUTi versus generalizable to other evidence-based psychosocial digital health interventions. Responses will next be coded inductively using thematic text analysis[89–91] to identify themes related to caregivers' barriers to and motivations for SHUTi uptake and usage, as well as how caregiver-specific tailoring may affect each of those constructs. Each response will be coded by two independent coders with discrepancies resolved by consensus. The coding team will iteratively determine a set of codes; identify, review and name themes; and synthesize data into final actionable recommendations for tailoring SHUTi and other digital health interventions for caregivers.

Findings and resultant recommendations will be returned to caregivers for synthesized member checking[92]:
(1) A concise report of results will be sent to caregivers;
(2) Caregivers will review the report and comment on how results compare/contrast with their experiences and needs; and
(3) Caregivers' returned responses will be coded to ascertain level of resonance between caregivers' reported experiences and the researchers' original results. Findings and recommendations will be revised according to synthesized member checking results.

To test whether the effects of SHUTi on cognitive mechanisms (i.e., more adaptive sleep beliefs, internalized sleep locus of control) are associated with caregiving context, a continuous regression model will be computed for each user and environment characteristic on each cognitive mechanism assessed at post, controlling for pre-assessment level of the mechanism.[93] Caregivers who are SHUTi users (incomplete and complete; not non-users) will be included, and models will control for level of SHUTi engagement and pre-specified covariates, with significance set at $p< .05$.

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 Informed Consent Document and Process

Once a potential subject is identified, they will be interviewed either by phone or in-clinic in a quiet and private place and may have family or friends with them if they choose. . Once the consent has been read the person obtaining consent will summarize the consent form verbally, asking open ended questions to determine if the potential subject understands what is being covered in the consent form. Questions might include:

- Would you summarize for me what you believe what would be asked of you if you are in this study?
- Would you benefit from this study?
- What do you feel are the risks of being in this study?

Potential subjects will be given an opportunity to ask questions. Their level of understanding will dictate how much time will be spent covering each item. Once all of their questions have been answered, if they decide to participate, they will be asked to sign the consent form, either by paper copy if in-clinic or through HIPAA-compliant DocuSign if by phone. The person obtaining consent will sign the form and subjects will be given a copy of the signed consent form (paper if in-clinic; PDF by email if by phone). Study procedures will then begin.

11.2 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. Consents will be maintained in a confidential manner in accordance with the code of federal regulations and HIPAA. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

The study monitor, representatives of the Institutional Review Board (IRB), regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

11.3 Safety Oversight

The study PI will be responsible for the safety oversight for this trial. AEs will be monitored throughout the study.

11.4 Site Monitoring

This study does not include a phase III clinical trial and therefore does not require an independent data and safety monitoring board. Project investigators will help ensure the safety of participants, as well as the validity and integrity of the data, by discussing project updates at the ongoing twice-monthly study meetings. At these meetings, we will review study progress and address any issues with the research procedures and database. Separate consultation will be sought with the study biostatistician regarding data issues. Twice-monthly supervision meetings will be held with the trained research study assistants at UVA and Pitt (convened via videoconference). Discussion at study meeting, separate consultations, and study staff supervision meetings with key personnel will cover:

1) recruitment, consent, and enrollment;
2) unanticipated problems, serious and unexpected adverse events, concluding with the safety procedures used to handle and minimize the occurrence of adverse events; and
3) procedures for data collection, data entry, and data storage. Procedures can always be modified to enhance the safety of the study if needed. All staff with access to data will have completed extensive human subjects protection training through the Collaborative Institutional Training Initiative (CITI) training program.

11.5 Data Handling and Record Keeping

11.5.1 Data Collection and Management Responsibilities

All possible precautions will be set in place in order to prevent loss of confidentiality through rigorous data security measures. All study data collected will be stored electronically on a UVA protected network drive and accessible only to the PI and essential members of the research team. Survey data will be collected via an online survey tool certified for use with HIPAA-regulated personal health information (PHI) and protected by the University's clinical firewalls. A password-protected list matching names with code numbers will be kept in a separate computer file and folder from the one where the data is stored. If a person agrees to participate in the study, all questionnaires will be labeled with the participants' study ID number, not their name or any other identifiable information. All identifiable data (e.g., phone number, email addresses) will be kept private on the UVA network drive and a password protected spreadsheet.

11.5.2 Study Records Retention

Record retention will be in accord with 21 CFR 312.62 and HIPAA regulations.

11.5.3

Type of Event	To whom will it be reported:	TIME FRAME FOR REPORTING	HOW REPORTED?
Any internal & external event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVA protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call
Internal & External, Serious, Unexpected and related adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. Unanticipated Problem Report Form
Protocol Deviations/Noncompliance *The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.* **OR** **Protocol Exceptions** *See definition- only allowed if there is a commercial sponsor*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Deviation, Noncompliance and Protocol Exception Reporting Form Protocol Deviation Protocol Exception Reporting Form

or a DSMB that has granted the protocol exception.			
Data Breach	The UVA Corporate Compliance and Privacy Office ITC: if breach involves electronic data UVA Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVA Corporate Compliance and Privacy Office- Phone 924-2938 **ITC:** Information Security Incident Reporting procedure, https://security.virginia.edu/report-information-security-incident UVA Police-Phone- (434) 924-7166

Reporting Requirements for the non-UVA site

Type of Event	To whom will it be reported:	TIME FRAME FOR REPORTING	HOW REPORTED?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVA protocol*	UVA study team/ Data Coordinating Center (DCC) UVA lead site or DCC will report to the IRB-HSR per table above	Within 24 hours	Written documentation
Internal, Serious, Unexpected and related adverse event	UVA study team/ Data Coordinating Center	Within 7 calendar days from the time the study team received	**Written documentation.**

	UVA lead site or DCC will report to the IRB-HSR per table above	knowledge of the event. *Timeline includes submission of signed AE form.*	**May use the** Relying Site Serious Adverse Event Reporting Form**.**
Unanticipated Problems that are not adverse events or protocol deviations This might include a Data Breach.	UVA study team/ Data Coordinating Center UVA lead site or DCC will report to the IRB-HSR per table above	Within 7 calendar days from the time the study team received knowledge of the event.	**Written documentation.** **May use the** Relying Site Unanticipated Problem Reporting Form
Protocol Deviations/Noncompliance *The IRB-HSR only requires that MAJOR deviations be reported, unless otherwise required by your sponsor, if applicable.* **OR** **Protocol Exceptions** *See definition- only allowed if there is a commercial sponsor or a DSMB that has granted the protocol exception.*	UVA study team/ Data Coordinating Center UVA lead site or DCC will report to the IRB-HSR per table above	Within 7 calendar days from the time the study team received knowledge of the event.	**Written documentation.** **May use the** Relying Site Protocol Deviation/Exception Reporting Form
Data Breach	Per local relying institution requirements The UVA IRB-HSR only needs to be notified of any data breach that meets the criteria of a UP	Per local relying institution requirements	Per local relying institution requirements.

12 REFERENCES

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13 APPENDICES

13.1 Schedule of Activities (SoA)

Procedures	Eligibility / Enrollment Day 0	Pre-Assessment Day 0 + 14 Days	SHUTi intervention period Completion of sleep diaries	Post-assessment 9 weeks post-SHUTi initiation +14 days
Eligibility screening	X			
Informed consent	X			
Pre-assessment (online questionnaires)		X		
Baseline sleep diaries		X		
Access to SHUTi (study intervention)			X	
Post-assessment (online questionnaires)				X
Follow-up sleep diaries				X

Data and Safety Monitoring Plan: IRB-HSR serves as sIRB of Record

13.1.1.1.1.1 DEFINITIONS:

1.3 What is the definition of an <u>unanticipated problem?</u>

Do not change this answer

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studies
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others

<u>Additional Information:</u> see the IRB-HSR website at Protocol Deviations, Non-compliance and Protocol Exceptions

1.4 What is the definition of a Protocol Exception?

__X___NA- No outside sponsor

_____Protocol has a sponsor or a Data & Safety Monitoring Board (DSMB) outside of UVA. Protocol exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects. Exceptions are planned, and the investigator gets approval from the sponsor ahead of time. Such a request should be rare and justified in terms of serving the best interests of the potential study participant.

1.5 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*

13.1.1.1.1.2 2. IDENTIFIED RISKS AND PLANS TO MINIMIZE RISK

_____NA- PI is not the overall person overseeing the safety data for this study.

___X__All adverse events

We will monitor the safety of participants and the security and integrity of data through several, interrelated strategies. No serious problems are anticipated, but should they occur while the subject is in the protocol they will be reported to the IRB according to policies. Any unanticipated problem or serious and unexpected adverse events will require re-evaluation of the risk of the study. As PI, Dr. Shaffer will be the person to whom all unanticipated problems or serious and unexpected adverse events, whether psychological or medical, are initially reported. Dr. Shaffer is a licensed clinical psychologist who can evaluate whether the events are SAEs or AEs. Dr. Shaffer will be responsible for ensuring that all unanticipated problems or serious and unexpected adverse events are reported within 48 hours to the IRB and NCATS. We will, of course, monitor the profile of adverse events carefully and take any necessary steps needed to maintain participant safety. Any change to the procedures will be forwarded to the IRB for approval. Additionally, we will submit an annual report to the NCATS Project Officer summarizing all adverse events.

There are a number of procedures in place to protect against possible risks:

(1) Loss of privacy: All possible precautions will be set in place in order to prevent loss of confidentiality. Risks will be minimized by the following considerations: all study data collected will be stored electronically on a UVA protected network drive and accessible only to the PI and essential members of the research team. Qualtrics for Highly Sensitive Data will be used to administer questionnaires: this web-based survey tool is frequently used in behavioral health research and is HIPAA compliant. The data will be password protected. During data summarization and analysis, individual participants will be identified by code number only. No data identifying individual participants will be published or disclosed to third parties without prior consent of the participant. A password-protected list matching names with code numbers will be kept in a separate computer file and folder from the one where the data is stored. If a person agrees to participate in the study, all questionnaires will be labeled with the participants' study ID number, not their name or any other identifiable information. Participants will be informed that they can choose to not answer any questions for any

reason. All identifiable data (e.g., phone number, email addresses) will be kept private on the UVA network drive and a password protected spreadsheet.

(2) Initial discomfort/embarrassment: For all participants, completing questionnaires may cause some distress or discomfort; however, past research has shown that such distress is usually minimal and transient. Participants are informed that they may withdraw from the study at any time or not answer questions they do not wish to address.

(3) Internet 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 via the Internet will be obtained through secured means and stored on private servers. All data on our servers are password protected and limited to authorized research personnel. The high-level architecture of the system allows us to separate 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 HIPAA compliant firewall where secured data reside, and only individuals who have onsite or VPN access 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 program. Data submitted by these users are captured and transferred to the secure server. Analyses will be conducted without identifiers.

(4) Initial tiredness: Participants who follow SHUTi recommendations to restrict sleep could initially feel more tired. To minimize the risk associated with sleep restriction, the system does not recommend participants restrict sleep to fewer than five hours. The initial assigned sleep window is also comparable to how much total sleep time the participant is already getting (based on diary data), but the sleep time is restricted to a smaller window (i.e., rather than allowing a participant to get 6 hours of sleep while spending 8 hours in bed, a participant may be asked to spend no more than 6 hours in bed). Participants will be told to avoid operating a car or other heavy machinery when they feel tired. To further minimize risks associated with sleep restriction, we will instruct participants that they may contact us if they have significant concerns. As needed, we will instruct participants to contact their primary care provider.

(5) Limited human element in provision of care: To minimize the risks associated with conducting a study online (i.e., more limited in-person assessment or no face-to-face treatment), participants will be instructed to contact study staff if they have any concerns or questions. This has been done successfully in all of our Internet intervention studies, with study staff interacting with participants in the participant's preferred method. Study staff are also well-trained to provide technical support. If any participant shows evidence of the need for immediate treatment (e.g., active psychosis, suicidal intent) at any time during the consent, assessment, and treatment periods, one of the investigators will be notified and

the patient will be referred for immediate psychiatric assistance. All participants will be able to access support for technical difficulties. All interactions will be carefully tracked (number of contacts, type of contact, and number of minutes spent on the contact). This information ensures clear communication and prompt responses with participants. It also allows us to evaluate whether outcomes are affected by interaction with study staff.

(6) Ethical and legal concerns regarding online intervention provision: We have worked extensively with the University of Virginia's legal counsel to ensure that ethical and legal issues are reviewed and addressed in our other Internet-based studies and will do so again for the proposed study. Participants will be instructed to talk to their Primary Care Physician (PCP) if they have any concerns or questions regarding website content. Participants will be required to indicate that they have read and accept language that states they should not consider the information in the application to be a replacement of medical advice, but should contact their PCP if they have questions or concerns.

_____Unanticipated Problems

__X___Protocol deviations/Issues of noncompliance

This study does not include a phase III clinical trial and therefore does not require an independent data and safety monitoring board. Project investigators will help ensure the safety of participants, as well as the validity and integrity of the data, by discussing project updates at the ongoing twice-monthly study meetings. At these meetings, we will review study progress and address any issues with the research procedures and database. Separate consultation will be sought with Mr. Camacho (statistician) regarding data issues. Twice-monthly supervision meetings will be held with the trained research study assistants at UVA and Pitt (convened via videoconference). Discussion at study meeting, separate consultations, and study staff supervision meetings with key personnel will cover: 1) recruitment, consent, and enrollment; 2) unanticipated problems, serious and unexpected adverse events, concluding with the safety procedures used to handle and minimize the occurrence of adverse events; and 3) procedures for data collection, data entry, and data storage. Procedures can always be modified to enhance the safety of the study if needed. All staff with access to data will have completed extensive human subjects protection training through the Collaborative Institutional Training Initiative (CITI) training program.

_____Audit results

_____Application of dose finding escalation/de-escalation rules

These should be outlined under 2.4.

_____Application of study designed stopping/decision rules

_____Early withdrawals

_____Whether the study accrual pattern warrants continuation/action

_____Endpoint data

__X___Other: Specify Answer/Response: Protecting against loss of confidentiality

All possible precautions will be set in place in order to prevent loss of confidentiality through rigorous data security measures. All study data collected will be stored electronically on a UVA protected network drive and accessible only to the PI and essential members of the research team. Survey data will be collected via the UVA Highly Sensitive Data Qualtrics portal, which is certified for use with HIPAA-regulated personal health information (PHI) and protected by the University's clinical firewalls. A password-protected list matching names with code numbers will be kept in a separate computer file and folder from the one where the data is stored. If a person agrees to participate in the study, all questionnaires will be labeled with the participants' study ID number, not their name or any other identifiable information. All identifiable data (e.g., phone number, email addresses) will be kept private on the UVA network drive and a password protected spreadsheet.

13.2 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
	9/2/21	Removed OnCore registration / line about treating physician	Removing OnCore participant registration – this is not required as it is expedited research. Removing "treating physician" as this is not applicable to the study.
	9/2/21	Added UVA Cancer Center recruitment database	Added recruitment method of sending letters to individuals previously indicating interest in contact for future research studies
	9/2/21	Added Karen Ingersoll, PhD	Added Karen Ingersoll, PhD as subinvestigator
