Telehealth CBT-L for Veterans using substances

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Abstract

Loneliness—a subjective emotional state characterized by the perception of social isolation—is a psychosocial factor that is associated with increased mortality, substance use, and is associated with precipitants of relapse among individuals with substance use disorders (SUD). Importantly, there are effective interventions that can be used to decrease loneliness; however, these have not been tested on Veterans with SUD who are lonely.

There are no studies that have tested a loneliness intervention in Veterans with SUD who are lonely, which may neglect a broader impact on mental and physical health. This study is ideally situated to generate new and important knowledge on the association of loneliness and SUD. This study seeks to address a transdiagnostic factor, which may improve engagement with social support thereby reducing substance use. An additional innovative aspect of this study is recruitment being conducted outside the VHA. This may increase access to care among those Veterans who are especially isolated.

We will initially conduct a small single-arm trial (n = 6) for further refinement. This trial will allow us to collect feasibility of treatment delivery, and treatment satisfaction and acceptability data to further refine the manual. With the refined manual Veterans with SUD reporting loneliness will be randomized to either CBT-L/SUD (n = 15) or CBT-SUD (n = 15). We will assess: (1) treatment acceptability, (2) participant adherence to treatment, and (3) therapist fidelity. We will also assess outcome measure completion percentage, means and standard deviations, and level of correlation of repeated measurement of primary loneliness outcomes and secondary substance use outcomes.

List of Abbreviations

CBT-LS: Cognitive-behavioral therapy for Loneliness

SUD: Substance Use Disorders

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Study Protocol

Protocol Title: Telehealth CBT-L for Veterans using substances

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2.0 Introduction

Substance use is a significant public health concern. Life expectancy in the United States had increased for over 50 years before slowing more recently and having a three-year decline from 2015-2017.[1] This decline is largely attributed to staggering increases in deaths of despair—drug overdoses, alcohol-related mortality, and suicide.[1,2] The rate of drug overdoses in 2017 was nearly 5 times higher than in 1999. The death rate from alcoholic liver disease increased 40%, with age-specific increases as high as 158% among adults ages 25 to 34 years.[1] Alcohol is estimated to be involved in nearly one-third of all suicides,[3] and the number of suicides involving opioids nearly tripled from 1999 to 2014.[4] The suicide rate among Veterans with opioid use disorders is now quadruple the overall rate of Veterans.[5]

The Veterans Health Administration (VHA) has taken an aggressive and comprehensive approach to respond to substance use-related morbidity and mortality.[6] This includes decreasing opioid analgesic prescribing, increasing non-pharmacological pain treatment, establishing clinical dashboard tools (e.g., REACHVET, STORM), and increasing access to effective medications for opioid use disorders and opioid overdose reversals among many others.[6-10] These approaches are significant, and at the same time, developing treatments focusing on novel therapeutic targets are critical in addressing substance use disorders (SUD) as Veterans with SUD continue to suffer from comorbidity and premature mortality. *Social factors, such as loneliness and social isolation, continue to plague people with SUD. Greater emphasis addressing these social stressors are essential to curb substance use-related morbidity and mortality.*

The 21st century has brought advances in technology improving our ability to connect and communicate with people from around the world. Despite advances to improve connection, there has been a global increase in loneliness.[11] The same technology aimed at increasing connection may be decreasing it for some.[12] Related social factors such as decreases in household and social network size, marriage rates, and religious affiliation rates are contributing to this through diminished opportunities for social connection.[13] Deaths of despair also have a large impact on communities through the degradation of social networks and social cohesion.[14] Additionally, with measures aimed at increasing social distancing due to the COVID-19 pandemic, many people have become further isolated, have fewer economic opportunities, and have reduced access to adaptive coping strategies and treatment.[15,16]

Loneliness—a subjective emotional state characterized by the perception of social isolation[11]—is a critical social factor that can have a significant impact on substance use. Loneliness is evident across the lifespan and occurs at higher rates among those with psychiatric disorders, people who are objectively isolated, and people with chronic illnesses.[11] Among a cohort of over 25,000 Veterans, 44% reported feeling lonely at least sometimes in the last month, with other studies among civilians estimating the prevalence from 20-33%.[17-19] Loneliness has a profound impact on well-being. A meta-analysis of 70 studies found that loneliness increases the odds of mortality by 29% even after accounting for key risk factors.[20] Researchers have estimated that the impact of loneliness on mortality is comparable to that of

obesity or smoking 15 cigarettes a day.[21] Loneliness has deleterious effects on physical and mental health, increasing the risk for a constellation of chronic diseases and the development and exacerbation of psychiatric disorders and substance use.[22,23] Loneliness is positively associated with suicidal ideation and suicide attempts.[22] In a study among Veterans with depression being seen in primary care, loneliness (and not other social connection constructs) were associated with increased depression, endorsement of suicidal ideation, and reduced treatment seeking intentions.[24]

Loneliness and social isolation are critical clinical endpoints that must be addressed among Veterans with SUD to reduce relapse and preventable deaths. A considerable proportion of individuals with SUD experience loneliness. A vicious cycle among people with SUD develops as social contact becomes less rewarding and stigma distances people with SUD from others, including social support. This social isolation then drives further substance use.[25] A study among treatment seeking patients with an opioid use disorder showed that nearly three-fourths of women and over two-thirds of men reported *moderate to severe* loneliness.[26] Nearly 40% of people with an alcohol use disorder reported feeling lonely and isolated at least sometimes.[27] Loneliness among those with SUD have increased risk of relapse and other negative consequences.[28] Relative to patients with SUD who do not report loneliness, those reporting loneliness have lower quality of life and life satisfaction, and more mood disorder symptoms, non-suicidal self-injury, and suicide attempts.[28-32] Loneliness among individuals with SUD is also associated with greater pain severity and sleep disturbance, two precipitants of relapse.[33,34] People with SUD report loneliness as an important reason for craving and among the most common reasons for relapse.[35,36] Loneliness is higher earlier in recovery and predicts shorter length of stay in treatment.[28] A qualitative study identified a subgroup of individuals using heroin who were characterized as being more socially disconnected and these individuals have more cognitive barriers to engaging in methadone maintenance (e.g., treatment harms outweigh the benefits) compared to other subgroups.[37] *Addressing loneliness among Veterans with SUD can reduce risk factors for relapse or continued use and have a significant positive impact on how a person develops, maintains, and utilizes social support, including treatment seeking—all of which are essential factors in reducing substance use.*[38-41]

3.0 Objectives

The proposed study will provide critical feasibility and acceptability data on telehealth Cognitive-Behavioral Therapy for Loneliness for SUD (CBT-L/SUD) among Veterans with SUD who report loneliness. We will conduct a small single-arm trial (n = 6) for refinement of the intervention and study procedure. With the refined manual, Veterans with SUD reporting loneliness will be randomized to either CBT-L/SUD (*n* = 15) or CBT-SUD (*n* = 15). The specific aims are as follows:

Aim 1: Refine the CBT-L/SUD manual by conducting a one-arm trial among Veterans with SUD who report loneliness (n = 6). *We will deliver CBT-L/SUD as part of a small, single-arm trial. This trial will allow us to collect feasibility of treatment delivery, and treatment satisfaction and acceptability data to further refine the manual.*

Aim 2: Randomize participants to receive either CBT-L/SUD (n = 15) or CBT-SUD (n = 15) to assess feasibility and acceptability among Veterans with SUD who report loneliness. *We will assess: (1) treatment acceptability, (2) participant adherence to treatment, and (3) therapist fidelity. We will also assess outcome measure completion percentage, means and standard deviations, and level of correlation of repeated measurement of primary loneliness outcomes and secondary substance use outcomes.*

4.0 Resources and Personnel

The study team consists of Drs. Ashrafioun, Allan, Stecker, Mr. Bogan, research therapists (TBD) to deliver the intervention, and additional research assistants as needed. Research therapists will have at least a master's degree in a counseling/health-related field and prior CBT training Drs. Allan, Stecker, and Ashrafioun will be in charge of executing the scientific objectives of this project. Mr. Bogan will serve as project coordinator. Mr. Bogan will assist in IRB documentation, participant payment and tracking, advertising, and conducting eligibility screening. Mr. Bogan will also complete screening and consent procedures, and complete assessment packets by telephone with participants at baseline, post-intervention and the 30-day follow-ups. Study therapists will deliver the intervention to 36 participants (6 for one arm trial, 30 for small RCT).

5.0 Study Procedures

5.1 Study Design

Study sample: We will initially recruit 6 veterans who screen positive for loneliness and screen positive for active substance use disorder to receive CBT-L. Once these 6 veterans have completed study procedures, we will recruit an additional 30 to be randomized to either CBT-L or CBT-L/SUD. This cohort will be randomized 1:1. The study will take place at the VA Center of Excellence for Suicide Prevention. Participants meeting study eligibility criteria will be enrolled in the one-arm trial to receive CBT-L.

Screening: The project coordinator will screen by phone following a script. Potential participants will provide verbal consent to complete the screening measures. Those individuals meeting eligibility who are interested in participating will be scheduled for a phone-based consent and baseline assessment appointment. Based on our past experience, we expect approximately 25% of all participants who complete the screening to be eligible to and interested in participating. Therefore, we expect to screen no more than 500 participants to reach our sample of 36.

Assessments and Intervention*:*

Participants will be enrolled following consent and will complete the baseline assessment. Participants will schedule a convenient time for their phone-based intervention sessions. Mid-treatment, post-treatment and 30-day post-treatment follow-up assessments will also be conducted by phone, depending on the phase of the study. Participants will be paid $40 each assessment completed. The post-treatment assessment will also include an exit interview for participants to describe acceptability of the intervention. Total compensation will be up to $80 for the pilot phase, and $120 for the randomized phase.

CBT for Loneliness for Substance Use Disorders (CBT-L/SUD):

The study team recently created a CBT-L/SUD manual (see **Appendix**) starting from a translation of the Kall et al. CBT-L manual as the base.[42] We then incorporated relevant content and worksheets from the VHA Brief CBT manual and worksheets from CBT-SUD into the CBT-L base.[43,44] The study team met and discussed ways to integrate content into the CBT-L manual based on our conceptual model, existing literature on substance use and loneliness, and other pertinent content from the VHA Brief CBT manual (e.g., material from behavioral activation) and CBT-SUD manual (examples of negative thoughts; case history).

The full draft of the manual can be found in the **Appendix** with a broad overview of session-by-session content below. CBT-L/SUD is a brief, patient-centered, tailored, one-on-one, 8-session intervention. Each weekly session is 45-60 minutes delivered via telehealth. Participants will initially be presented with education on activating events eliciting thoughts, behaviors, and emotions that serve to perpetuate loneliness and substance use (i.e., the CBT model). Sessions will then focus on identifying and changing thoughts that contribute to loneliness and substance use. If a participant states "No one wants to be around a drunk like me," or "my drug use always makes me feel better when I'm alone." They would be asked to estimate the accuracy of the thought and to dispute it. For example, the original thoughts might be altered to "My buddy called me last week, so apparently he wants to be around me," "there's much more to me than just my drinking," "Shooting up only made me feel lonelier," and "I enjoyed it more when I got coffee with my brother." Importantly, CBT-L/SUD encourages participants to test these beliefs in safe, but real-world experiences (e.g., going to get coffee and noting that it reduced loneliness). Exposure and behavioral activation are used to approach avoided behaviors and activities (e.g., social interactions in sober environments) and to increase the participant's general activity level to improve mood. By increasing activity level, particularly through engaging in pleasant social activities, the participant's mood may improve by decreasing avoidance, increasing the potential for social contact, reducing risk of substance use, and increasing self-efficacy to engage in such activities without the use of substances. In the final session, the participant identifies ways to cope with loneliness-related problems by identifying strategies, evaluating the potential solutions, and selecting a plan to implement the strategies. This discussion will occur in the context of preventing a return to behavioral inactivation and allowing maladaptive thinking to drive poor coping, further maladaptive thinking, and lack of activity. Throughout the intervention, we emphasize (1) not engaging with individuals who will threaten recovery, and (2) not entering situations or contexts that place them at unnecessarily high risk of use (e.g., meeting people a bar).

- Session 1: CBT Model & Goal Setting
    - Substance use integrated into CBT model; goals also associated with addressing SUD-relevant goals)
- Session 2: Identifying & Challenging Thoughts I
    - Substance-use related thoughts perpetuating loneliness; loneliness-related thoughts perpetuating loneliness
- Session 3: Identifying & Challenging Thoughts II
    - Continued focus on substance use- and loneliness-related thoughts perpetuating substance use and loneliness
- Session 4: Assertiveness Training
    - Teaching effective communication and conflict resolution
- Session 5: Exposure & Behavioral Activation I
    - Incorporating sober activity into exposure and behavioral activation; considering difficulty of exposure when sober

- Session 6: Exposure & Behavioral Activation II
    - Incorporating sober activity into exposure and behavioral activation; considering difficulty of exposure when sober
- Session 7: Problem Solving
    - Developing a plan to remain sober while implementing or practicing CBT skills and increasing social interactions
- Session 8: Review & Relapse Prevention
    - Review is specific to new content, using skills for CBT-L to address and avoid slips and/or relapse

CBT-SUD: We will utilize the DeMarce and colleagues CBT-SUD manual developed for Veterans, which is designed for flexibility and individualization.[44] In order to maintain consistency with CBT-L/SUD, CBT-SUD will be delivered over 8, ~45-60 minute sessions. CBT-SUD teaches skills to increase awareness and address thoughts, behaviors, and emotions that contribute to the maintenance of substance use. There are three phases of treatment: preparing and planning for change (1 session), cognitive-behavioral strategies (6 sessions), and maintaining change and termination (1 session). Phase 1 includes building support, case conceptualization, building motivation, and orientation to CBT. Phase 2 will continue case conceptualization and building motivation, while introducing and practicing cognitive-behavioral strategies. Sessions include (1) recognizing and dealing with craving, urges, and triggers, (2) learning refusal and listening skills, (3) managing mood, (4) social and recreational counseling, (5) support for sobriety, and (6) problem solving. Phase 3 involves review of skills to help maintain treatment gains and ending treatment. The manual is included as an Appendix.

5.2 Recruitment Methods

Recruitment and retention procedure: Participants will be recruited using Internet social media websites (e.g., Facebook, craigslist) and select print/web portals that have been used successfully in several large studies. Advertisements will include a link to a study landing page with study information and blank entry forms for interested Veterans to enter contact information through VA Qualtrics on Fedramp, a secure, FISMA-compliant server used across government agencies with an authority to operate with the VA. We plan to enroll 36 participants in the protocol overall.

Participants will also be recruited through a data access request using data from the Corporate Data Warehouse. CDW contains financial, enrollment, demographic, diagnostic, treatment utilization, and other data across Veterans from 1979 to present. All study staff will be trained on accessing these records by Dr. Ashrafioun. Joint Longitudinal Viewer will be used to access medical records to prioritize recruitment of Veterans with an active SUD. This pre-screening will help reduce Veteran burden and unnecessary contact of Veterans who would not be eligible. Participants identified through this method will be screened using the same criteria as those recruited through social media websites and select print/web portals as described above. Potential participants will be mailed a personalized letter describing the study and provided with a toll-free number so that they can contact study staff if they are interested in participating as well as opt out of future contact. Potential participants may be recruited from other studies that are IRB approved following completion of those other studies or if deemed ineligible. Only study staff that are approved on those studies will recruit those participants. Providers may also refer participants to the study by emailing the research staff/team. Providers will be given the

approved recruitment letters that are provided to Veterans as well as the approved study landing page for information (content can be found on p. 54 of the approved advertising pdf).

Participants will receive compensation for their participation in the study. The compensation amount will be based on the schedule that follows:

Baseline Assessment	$40
Post-treatment Assessment (w/in a week)	$40
30-day Assessment (RCT only)	$40

Therefore, the total compensation for completing all the study components would be $80 for the Aim 1 one-arm trial and $120 for the Aim 2 RCT. Payments will be made via direct deposit or check following each study procedure listed above. Participants who do not complete the entire study for any reason will receive compensation for the components that were completed per the above schedule of payments.

5.3 Informed Consent Procedures

There are two phases where informed consent could be obtained, when completing the screening for eligibility and when enrolling into the study following the screening and if eligibility criteria are met. Verbal consent to participate will be obtained for the screening and baseline appointment. Informed consent will be obtained by study personnel trained in human subjects' protections requirements and how to obtain and document informed consent.

5.4 Inclusion/Exclusion Criteria

Inclusion criteria: Participants will include men and women who:

- Are English-speaking
- Are 18 years of age or older
- Have access to a phone or computer
- Screen positive for active SUD of at least moderate severity based on the M.I.N.I.
- Screen positive for loneliness by scoring at least a T-score > 60 on the NIH Toolbox loneliness scale

We will use the Veteran Verification screening for Veterans recruited through social media advertising to help confirm Veteran status.

Exclusion: Veterans will be excluded on the basis of:

- Does not understand informed consent

Pregnant women will not be excluded from this study as no invasive medical procedures are being performed and there is no known risk to the mother or the fetus of the proposed interventions. The study will not include prisoners or institutionalized Veterans.

5.5 Study Evaluations

Loneliness: The 20-item Revised UCLA Loneliness Scale will be our primary outcome measure.[45] We will use the 5-item NIH Toolbox Loneliness Scale[46] as our loneliness screening measure. The NIH Toolbox Loneliness Scale is correlated highly (r = .80) with the Revised

UCLA Loneliness Scale.[24,46] T-scores >60 indicate loneliness scores 1 standard deviation above the mean and will be used to assess eligibility.[47]

Quality/Quantity of Social Interactions: The Duke Social Support Index (DSSI) assesses several domains of perceived social support, including social network size, social interaction, social satisfaction, and instrumental social support. Research supports the psychometric properties of the DSSI scales.[48-50] *Belongingness and Burdensomeness*: The Interpersonal Needs Questionnaire (INQ-12) assesses thwarted belongingness (i.e., an unmet need to belong) and perceived burdensomeness (i.e., feeling like a burden to one's social support network). Research supports the scale's psychometric properties.[51]

Substance use: We will use the *Timeline Follow Back (TLFB)*[52] to assess quantity and frequency of substance use, and percent days abstinent. For the baseline assessment, participants will complete the TLFB for the past 3-months. Facilitating participant recall, the TLFB will be completed at each assessment so there are shorter intervals. *Consequences of substance use*: The Inventory of Drug Use Consequences (InDUC-2) will be used to assess drug use consequences in the following domains: impulse control, social responsibility, physical, intrapersonal and interpersonal.[53] Consequences will be assessed for the last 3 months at baseline and the follow-up will be since the previous assessment.

Other key descriptive variables: Treatment utilization: We will assess participant past and current substance use and mental health treatment utilization at baseline and follow-up. We will also assess primary care and specialty medical care visits, both within and outside the VA. This will be done using a modified version of the Treatment Services Review (TSR).[54] *Quality of life:* The PROMIS Profile-29 will be used to assess the following: anxiety, depression, physical function, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference.[55] *Demographics and military background.* At screening, we will assess participants' branch, deployment history, gender, age, educational background, employment, income, race, ethnicity, and marital and cohabitation status.

5.6 Schedule of Assessments

Schedule of Assessments – One Arm Trial			
Measures	**Screening**	**Baseline**	**Post-Intervention**
Informed Consent - Verbal	X		
Eligibility Review	X		
Demographics and Military Background		X	
Oral Fluid Samples		X	X
NIH Toolbox Loneliness Scale		X	X
Timeline Follow Back (TLFB)		X	X
Revised UCLA Loneliness Scale		X	X
Duke Social Support Index (DSSI)		X	X
Treatment Services Review (TSR)		X	X
PROMIS-29		X	X

Inventory of Drug Use Consequences - InDUC-2		X	X
Interpersonal Needs Questionnaire-12		X	X
Exit Interview			X

Schedule of Assessments - Randomized Clinical Trial				
Measures	**Screening**	**Baseline**	**Post-Intervention**	**30-day Follow-up**
Informed Consent - Verbal	X			
Eligibility Review	X			
Demographics and Military Background		X		
NIH Toolbox Loneliness Scale		X	X	X
Timeline Follow Back (TLFB)		X	X	X
Revised UCLA Loneliness Scale		X	X	X
Duke Social Support Index		X	X	X
Treatment Services Review (TSR)		X	X	X
PROMIS-29		X	X	X
Inventory of Drug Use Consequences (InDUC-2)		X	X	X
Interpersonal Needs Questionnaire-12		X	X	X
Exit Interview			X	

5.7 Data Analysis

We will track rate of recruitment per week, and the percentage of participants who complete the protocol, and each follow-up. Participant treatment adherence will be assessed by tracking attendance and homework completion. Session-by-session participant feedback will be used to examine potential reasons for drop-out and non-adherence to inform our small RCT. Therapist adherence scores for the individual sessions and the overall interventions will be assessed as the percentage of the content delivered. Interrater reliability for fidelity will be assessed using intra-class correlation coefficients. We will assess the internal consistency of competence using Cronbach's alpha. Treatment acceptability will be assessed with the modified AARS and exit interview for a richer understanding. For participants who choose to withdraw prior to completing the full protocol, attempts will be made to conduct exit interviews to assess treatment experiences and reasons for early withdrawal. Interviews will be audio-recorded and transcribed. Interview data will be analyzed using matrix analysis,[56-58] a systematic technique for data reduction to thematically organize and analyze data using rows, columns, and cells of a table. This process is time efficient, aligns well with results of in-depth analyses, allows for accurate summarizing of data, and facilitates participant comparisons.[57]Matrices are also an effective way to share findings with interdisciplinary team members for discussion.[56] Following

the analyses, these matrices will be reviewed by the investigative team and expert panel in preparation for finalizing the intervention.

Consistent with descriptive analyses for pilot studies,[59] measure completion percentage and means and standard deviations for outcomes will be calculated at each assessment, including change scores and correlations across timepoints. We expect large standard errors due to small sample size. Distribution of scores will be examined to better evaluate how to analyze these data in future studies (e.g., dichotomizing/ categorizing vs. continuous). For continuous outcomes, Hedge's *g* will be calculated to identify a range of the pre-post effect size. Although such calculations are of limited benefit in determining the effect of the intervention, they can be helpful in identifying outcomes that are less sensitive to change. Correlations among baseline variables will be calculated to assess the potential for variables to be included as covariates in the larger trial. This may also be useful in identifying potential moderators and mediators for the future larger trial. For data quality and handling of missing data, descriptive statistics will help identify out of range values and outliers. We will examine bias in retention rates at both the univariate and multivariate level of analyses

Data storage, security, and confidentiality

Several procedures for protecting participant confidentiality will be implemented to reduce the risk of revealing participant identity. All informed consent forms will contain identifying information. In order to ensure confidentiality, each consent form will be labeled with a numeric identifier and will be stored in a double-locked file. These will be stored in separate double-locked files from other study materials. As noted in the Data Transport Memorandum, locked courier bags will be used to transport any sensitive study information (e.g., consents) outside VA.

The VA Informatics and Computing Infrastructure (VINCI) will be used for the storage of study data. VINCI is a major informatics initiative of the Department of Veterans Affairs (VA) that provides a secure, central analytic platform for performing research and supporting clinical operations activities. It is a partnership between the VA Office of Information Technology (OI&T) and the Veterans Health Administration Office of Research and Development (VHA ORD). VINCI includes a cluster of servers for securely hosting suites of databases integrated from select national VA data sources. VINCI servers for data, applications and virtual sessions are physically located at the VA Austin Information Technology Center (AITC), located in Austin, Texas. This secure enclave with 105 high-performance servers and 1.5 petabytes of high-speed data storage has multiple layers of security and disaster recovery to prevent data loss.

Study data will be kept in accordance with the Department of Veterans Affairs Record Control Schedule 10-1 (RCS 10-1). Storage and transfer of any Personally Identifiable Information (PII) or Protected Health Information (PHI) must be done in accordance with applicable VA and VHA policies and directives, state and federal regulations, and applicable statutes including the Health Insurance Portability and Accountability ACT (HIPAA). Unless explicitly requested and approved by data stewards, all sensitive patient data must remain on VINCI project servers and only aggregate data without PII / PHI may be transferred from VINCI.

Prior to being uploaded to VINCI for analysis, data will be stored on a secure VA server, which is password protected, and to which only IRB approved VA research personnel have access. Should any identifiable information need to be shared between research sites, research teams will utilize a secure, SharePoint site or electronic communication with PKI encryption. Any identifiable paper data will stored in two separate locked file cabinets (one for informed consents and the other for paper questionnaire data) in the offices of the Center for Excellence for Suicide Prevention at the Canandaigua VAMC. After a participant completes the study, any identifiers will be removed from the paper questionnaire data immediately. Data analysis will occur in the VINCI framework.

5.8 Withdrawal of Subjects

Participants who wish to withdraw may do so at any time without affecting their medical care or participation in any other study. Participants will be informed of any new information during the course of the study which may affect their condition or influence their willingness to continue in this study. Finally, based on decisions made by the Principal Investigator, participants may be taken out of the study because of unanticipated circumstances such as extreme distress. That is, they may be withdrawn from the study if we judge that participating is not in their best interest.

6.0 Protection of Human Subjects

Protection of Human Subjects

Risk to Participants

Human Subjects Involvement and Characteristics. The purpose of this study is to assess the feasibility and acceptability of Cognitive-Behavioral Therapy for Loneliness for Substance Use Disorders (CBT-L/SUD) among Veterans with SUD who are lonely. After an initial refinement phase during which 6 Veterans will complete the study protocol, a total of 30 participants will be recruited across the US and randomized to receive either CBT-L/SUD (n = 15) or Cognitive-Behavioral Therapy for Substance Use Disorders (CBT-SUD; n = 15).

According to 2018 data from the National Survey of Drug Use and Health, 92.9% of respondents who had ever served in the military and had SUD were men. We expect to have a greater number of women compared to this proportion given that loneliness is more common among women and given increased recruitment of women. SUD prevalence increases with age as those with SUD who had ever served in the military was least common among ages 18-25 (1.3%) and 26-34 (6.8%) and most common among those 35-49 (16.4%) and 50+ (52.1%). We expect there to be relatively greater proportions of younger age and older age groups (rather than middle age groups) because loneliness is more common among those age groups.

Source of Materials. Study materials will include self-report questionnaires. The materials will be collected for study purposes only. Information collected will be stored in a locked filing cabinet in a locked office at the study sites that can only be accessed by members of the study team. *All electronic data* will be stored on VA Informatics and Computing Infrastructure (VINCI) project servers. Only approved study team personnel who will be involved in data entry, management and analyses will be granted access to this data. All computers are password protected.

Potential risks.
Psychological distress. Anticipated risks to the participants from assessment procedures and therapy are minimal; however, participants may experience psychological distress, frustration, and/or fatigue. The semi-structured interviews, assessments associated with the intervention, and therapy sessions may encourage participants to recall personal events and life stressors that may evoke distress. Additionally, confidentiality may need to be breached if a participant poses a threat to him or herself or others, including child abuse.

Adequacy of Protection from Risk
Recruitment and Informed Consent.
All research staff will have completed appropriate and up-to-date training in research, research ethics and the proper conduct of research that includes common issues related to recruitment and informed consent.

Participants will be recruited using Internet social media websites, select web portals, and data accessed through the Corporate Data Warehouse. Advertisement will nationally target Veterans using opioids and who may be lonely. Targeted recruitment of women Veterans and Veterans of ethnic/racial minority status will also be used for advertisements. All sites will send participants to a study landing page, which serves as a central location for potential participants to follow-up with the study team via phone or completing and submitting an online form. Recruitment and informed consent procedures were designed to ensure patients do not feel like participation is required. Potential participants unable to understand the informed consent process will be excluded from participating. Screening interviews will be completed initially over the telephone (using a script) to assess eligibility criteria. Verbal consent will be obtained at this time to complete the screening. Participants screening positive for exclusion criteria will not be included in the study. For eligible and interested participants, a research coordinator will review the consent form and complete a brief questionnaire to ensure the potential participant understands the study. Verbal consent will be completed with procedures used by the PI that have been approved by our local IRB. Specifically, once eligibility is confirmed through screening, each of the essential elements of informed consent will be described to the Veteran to which they can provide verbal consent. The Veteran will be enrolled following consent.

Protection Against Risk.
Psychological distress. The potential risks are negligible. There are no known risks associated with interview procedures. Participants will be informed that they may feel slightly uncomfortable discussing some of their symptoms. Mild discomfort may be likely during the intervention session; however, this is unlikely to have a serious negative impact on the participant's well-being. Participants will be told they can withdraw from the study at any time. Participation or withdrawal from the study will not affect any benefits to which they are otherwise entitled. Special precaution will be taken to safeguard confidentiality. During assessments, if the interviewer is concerned about thoughts and planning of a suicide attempt, the interviewer will ask two follow-up questions: Do you have a desire to kill yourself that you think you might act on and Do you have a plan for killing yourself and intend to carry the plan out? With this information and available suicide assessment measures, the interviewer will evaluate the severity of the participant's suicide risk. If the participant is deemed to be at imminent risk, a safety plan will be initiated. All study staff will receive adequate training in suicidal ideation and risk assessment, and all work will be supervised by Drs. Ashrafioun, who is a licensed clinician.

If the interviewer is concerned about imminent risk, procedure for warm transfers to the National Suicide Prevention Lifeline (1-800-273-TALK; 988 by July, 2022). Emergency procedures will be initiated if patients are determined to be at imminent risk for suicide using the risk assessment described above. Participants determined to be at risk will be asked if they are willing to be transferred to the National Suicide Prevention Lifeline. Hotline responders are well trained in emergency procedures and have working protocols for locating callers and initiating rescues. All telephone sessions will be conducted using protocols to ensure that the clinicians' telephone is set up for transfers to the Crisis Line. Calls can be transferred with a four step process.

Warm Transfer Process

1. Press the **conference/add caller** button.
2. Dial 1-800-273-8255 press option 1 and a Crisis Line responder will answer.
3. Describe the participants risk and provide name and telephone number.
4. Pressing the **conference/merge calls** button and participants will be linked with Crisis Line

It is possible that participants may refuse to be transferred to the Crisis Line or hang up. As a result, participants will be asked to use a landline so that the number can be tracked to an address if emergency services are needed. For participants who only have a cell phone,

Interviewers will begin each session by asking the participant for the address from which they are calling so that the clinician can send help if it is needed. Because participants may give a false address, clinicians will consult with Lifeline responders who have a protocol for emergency responses for cell phone callers.

For participants that have a lower risk than imminent for suicide at baseline, our crisis plan will be consistent with guidelines employed by Dr. Ashrafioun as well as by the DoD/VA for people at low acute risk for suicide. This involves the following, which may or may not already be in place at the time the participant is deemed at low acute risk: (1) consider consultation with behavioral health specialty, (2) discuss safety and restriction of access to lethal means, (3) treat mental health and medical conditions, (4) address psychosocial needs, (5) encourage social support from friends, family, and/or community, (6) continue monitoring patient status and reassess risk in follow-up contacts, and (7) document risk assessment.

The Project Coordinator, research staff, and Research Therapists will receive extensive training in conducting screening for suicide risk assessment by Dr. Ashrafioun in consultation with Drs. Allen, Stecker, and Maisto. In addition, the Project Coordinator and Research Therapist will complete training webinars and extensive test-outs for fidelity.

Breach of Confidentiality. Statistical electronic data files will be kept VINCI project servers maintained by VINCI OI&T personnel and only summarized data without protected health information (PHI) will be downloaded from VINCI to local storage media. Research staff will use an audited VINCI download utility to move summarized data for reports, presentations and publications from VINCI servers to local storage media. The VINCI download utility provides an audit path including a copy of the downloaded material. The data extraction tool will be adapted for use with software directly available on the VINCI platform (e.g. Microsoft Word and Excel) and study data will be stored and maintained on VINCI. All study team personnel with access to sensitive patient data will stay current on their VA approved information security training and VA approved privacy policy training.

Data Safety & Monitoring Plan

Data Safety. To ensure safety of participants in the study proposed and validity and integrity of data collected, the PI (Ashrafioun) will oversee all data and safety monitoring functions and the research team will be advised that he will be the primary contact overseeing these activities. The investigators will meet regularly to monitor study progress and discuss the implementation of monitoring procedures. The PI will also meet regularly with the research staff to review monitoring procedures and ensure all efforts are being taken to minimize risks to participants. We will have an independent Data Safety & Monitoring Board (DSMB), appointed by HSR&D to help monitor safety issues. As indicated below, the PI will track all negative outcomes and incidents as well as conduct interim data analysis every 6 months after the study has started. The study design will be significantly modified (and even screening stopped) on the suggestion of the DSMB if the study is creating potential harm to our participants.

The PI will regularly oversee all aspects of the study, including participant recruitment, informed consent, data collection, management, and analysis, as well as regularly assess the risk/benefit ratio associated with participation in the study. All research staff will participate in an intensive

training to help them understand the importance of reducing the risk for participants and learning how to recognize and report any AE or SAE. SAEs may include: death, hospitalization due to worsening psychiatric symptoms or suicidal ideation, or all life threatening or disabling/incapacitating events among research participants. AEs may include, but are not limited to: physical injuries, worsened physical or mental health, or inadvertent disclosure of confidential research information.

If an SAE occurs, the PI will immediately contact the DSMB and IRB, followed by a written report in 24 hours. He will make a decision whether there is sufficient evidence to suspend data collection, allow for further IRB review, modify the protocol, or make other changes to reduce potential risk to participants. The study will resume based on agreement of the PI, the IRB chair, and the DSMB. In the event that an AE that is not an SAE is reported to the PI, the PI will discuss the event with the DSMB. Immediate evaluation will occur to determine if any extra steps can be taken to minimize the likelihood of that type of AE occurring again. If changes can be made, a report/amendment will be written and submitted to the DSMB and IRB.

As part of a standard practice, the PI will supervise the implementation of one audit within 4 months after study recruitment and one regularly per year afterwards of the materials collected and produced as part of the study at each site to ensure proper confidentiality and compliance with ethical principles, including confirmation of verbal consent, questionnaire data, and to make sure that the research staff are following established protocols. The PI will provide an annual summary report of all AEs to the IRB and the DSMB as part of the annual review. If no adverse events have occurred, the report will state, “No adverse events affecting human participants have occurred during this project year.”

Data Monitoring. To ensure adequate participant recruitment and enrollment, each week, the PI will discuss the current number of participants contacted, screened, and enrolled from each site and compare those numbers to the expected based on our preliminary data. If after the first 4 months, it appears we are not reaching our expected number of participants, the PI will discuss potential barriers/obstacles and solutions with the research team and DSMB. Discussions regarding recruitment and enrollment will continue at each meeting with the DSMB to ensure proper implementation of the study.

Data Safety & Monitoring Board. The purpose of the DSMB is to review protocols and consent documents for this study, monitor safety issues throughout the study, provide an overview of the quality of the accumulating data, and provide guidance on interim analyses and stopping rules. The DSM will be comprised of individuals appointed with by the funder (VA Health Services Research & Development) and will have no direct involvement in the study or conflict of interest with the research team conducting the clinical trial. The DSMB responsibilities will include:

(1) Protect the safety of the participants
(2) Review, provide approval/disapproval, and provide suggestions to protocols, consent documents, and plans for data safety and monitoring.
(3) Monitor, provide suggestions, and report on ethical issues regarding protection of human subjects, and advise on ethical issues regarding AEs. The DSMB will coordinate with the PI to report to the IRB any unanticipated problems involving risk. The DSMB will provide potential solutions or other appropriate actions (e.g., altering inclusion/exclusion criteria, changing consent documents).
(4) Ensure appropriate balance between clinical care, safety, and patient confidentiality.
(5) Monitor data the progress of the trial. The DSMB will periodically review outcome data for outcomes by treatment condition, including participant recruitment, retention, risks and benefits, and other factors that may affect outcomes. If differences in results

between conditions appear to be clinically significant, the DSMB will review whether the clinical trial should continue with or without further enrollment of new participants.

(6) Monitor and review any data relevant to quality control and safety.
(7) Make recommendations to the HSR&D about the continuation, termination, or changes to the trial based on benefits or adverse effects of the treatment.
(8) Communicate problems with the conduct, enrollment, sample size, and/or data collection to HSR&D

The PI will convene annually with the DSMB for the duration of the study. The meetings will be held via video teleconference. The Board Chair and PI will decide on the format of the meetings. Additional meetings will be held on the recommendation of the Board Chair and PI and meeting logistics will be based on clinical urgency and the availability of the DSMB. The PI will submit reports to the DSMB a week prior to the scheduled meeting. Reports will include all data up to and including 2 weeks prior to the reporting deadline (except for SAEs, which are to be reported within 24 hours of an event). For each meeting at which the study is to be considered or monitored, the PI will present an overall progress statement containing the assurance that the PI has considered the clinical trial's progress and that there is/is not evidence of safety issues that should be addressed by the DSMB. The reports will also include information related to problems in recruitment, biases in attrition, biases with respect to AEs, or other operational problems that affect the integrity of the study. At the additional request of the DSMB, interim analyses will be conducted to determine whether the emerging findings may lead to a discussion of discontinuing the trial early.

The DSMB will be kept apprised of all SAEs and AEs on an ongoing basis and will decide whether individual patients should be removed from the protocol. Although research staff, under the PI's supervision, are able to take whatever immediate action is necessary to safeguard the welfare of individual patients, the DSMB will be called on whenever possible to make decisions as a result of a SAE. There may be rare instances where some unanticipated situations occur that may affect participant welfare. In these situations, the Syracuse VAMC IRB or the DSMB may be contacted to help resolve the situation.

Adverse Events (AE). AEs may include, but are not limited to: worsened physical or mental health, or inadvertent disclosure of confidential research information. Serious Adverse Events (SAE) may include: death, hospitalization due to worsening psychiatric symptoms or suicidal ideation, or all life threatening or disabling/incapacitating events among research participants. Per IRB regulations, SAEs, any event resulting in a deviation from the study protocol (e.g., emergency hospitalization to address suicidal behaviors) or death will be reported to the PI within 24 hours and to the IRB in 48 hours. This will be completed in order to assess significance and determine an appropriate response. AEs that involve temporary distress will be noted by interviewers and provided to the IRB in an annual report.

Confidentiality of Records. Numerous protections are in place to reduce the likelihood of loss of confidentiality. All research data will be kept in locked filing cabinets in secure areas, absent of identifying information, and coded by research number only. Files containing items with identifying information will also be kept in locked filing cabinets, but these will be separate from cabinets containing data from this study. All electronic files, including therapy notes, will be maintained on a secure study folder behind the VA firewall. Only approved study team personnel will be granted access to this data. All identifiable information will be stored in a separate folder behind the firewall from the de-identified study ID and data.

Potential Benefits of Research to Participants and Others. There may be direct and/or indirect benefits of study participation. Participants are receiving a brief intervention that

addresses a transdiagnostic factor that may reduce both loneliness and substance use. Because this intervention can be used for both participants who are not engaged in treatment and for participants who are engaged in treatment, it may augment current services. Dissemination of the findings from the study will contribute to the extant literature, provide data to guide implementation, and may contribute to reducing loneliness and substance use.

Importance of Knowledge to be Gained. Understanding how to effectively address loneliness among Veterans with SUD is a critical approach to curb substance-related morbidity and mortality. Loneliness is associated with increased suicide risk, substance use, and key precipitants to relapse among people addicted to substances. Addressing loneliness has the potential to reduce substance use. The proposed study tests the 8-session CBT-L/SUD that will be refined as part of this study. This telehealth intervention targets cognitive biases, and avoidance of social interactions and enjoyable activities. We expect that this intervention will reduce loneliness, increase the quality and quantity of social interactions, and reduce substance use. Knowledge gleaned from this study will help inform a fully powered randomized clinical trial with the long-term goal of future implementation and dissemination efforts across numerous settings.

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