**Protocol Title:** Multi-site Pilot Trial of Strengths-based Linkage to Alcohol Care, Connect to Care (C2C)
**(Aim 2)**

**Funding Agency:** VA HSR&D IIR 20-058

**Principal Investigators:**
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## Abstract

Relatively few Veterans screening positive for hazardous drinking in primary care (PC) receive alcohol care in the year following alcohol screening. This suggests that existing options for linking Veterans screening positive for alcohol use disorder, including those with comorbid hazardous drinking and PTSD and/or depression (A-MH), within VHA are not effective. To that end, we have identified and propose to pilot test a promising evidence-based behavioral intervention, **Strengths-based Linkage to Alcohol Care (C2C, Appendix D).** (C2C) has the potential to increase access (linkage) to alcohol care options, as well as to improve drinking and mental health outcomes, among Veterans living with A-MH in PC.

The proposed project is highly innovative because it offers a solution to the critical gap in VHA care for Veterans in need of alcohol care. We propose to adapt, and pilot test an innovative, strengths-based approach, (C2C), to help Veterans with A-MH link to alcohol care and to improve their drinking and mental health outcomes. This strategy is designed to increase linkage to alcohol care that is both intensive enough to produce change, yet feasible enough to implement in busy clinical care settings that are overburdened and understaffed. (C2C) has been shown to be effective in the civilian population but has not yet been studied in VA. A highly innovative feature of (C2C) is that it supports Primary Care providers (PCPs) in linking Veterans with A-MH to alcohol care, which may help normalize conversations about patients' alcohol use and their care options. PC providers' lack of knowledge on how to treat hazardous drinking is a substantial obstacle to Veterans receiving alcohol care. Additional unique and innovative features of (C2C) are that it uses patients' self-identified strengths, abilities, and skills to help them link to an alcohol care option enhancing shared decision making. As VHA advances to Whole Health, (C2C) supports the provider and Veteran in providing patient centered care.

**Aim 1**: To adapt (C2C) for use among Veterans with A-MH being seen in the VHA Primary Care (PC) setting. (C2C) will be delivered by telephone or VA video connect (VVC). We are currently conducting qualitative interviews via focus groups (focus groups or individual interviews) with three participant groups: Veterans, PC staff, and VACO operational partners to ensure that the content and format of (C2C) are adapted so they are relevant and acceptable to these stakeholders VACO partners will include our existing partners (Drs. Post and Pomerantz) and other VACO policy leaders they identify as important to interview.

***Please Note, Aim 1 has received VA CIRB approval and is ongoing.***
***We are requesting approval for Aim 2.***

**Aim 2**: To determine (a) the feasibility of conducting a larger scale randomized controlled trial (RCT) to test the effectiveness of the (C2C) intervention, (b) the acceptability of (C2C) among Veterans with A-MH in PC, and to explore (c) the efficacy of (C2C) in this Veteran population. To achieve Aim 2, we will conduct a multi-site pilot RCT of (C2C) at two VA medical facilities, Little Rock, AR and Palo Alto, CA. To achieve Aims 2a-b, we will measure the feasibility (e.g., rates of enrollment, follow-up, and fidelity to the (C2C) intervention) of conducting a subsequent larger RCT to test the effectiveness and acceptability ((C2C) completion rates, satisfaction with (C2C)) among Veterans. To achieve Aim 2c, we will explore the efficacy of (C2C) to improve Veterans' linkage to and utilization of alcohol care, along with their alcohol and mental health outcomes, at 3-month follow-up. Additionally, we plan to conduct debriefing interviews with 20 participants assigned to the (C2C) condition to obtain data on its feasibility, acceptability, and perceived efficacy at 3-month follow-up.

List of Abbreviations

| | |
|---|---|
| A-MH | Hazardous drinking and PTSD and/or depression |
| ASI | Addiction Severity Index |
| ACM | Alcohol Care Management |
| ASSIST | Alcohol, Smoking and Substance Involvement Screening Test |
| AUD | Alcohol Use Disorder |
| AUDIT-C | Alcohol Use Disorders Identification Test-Consumption |
| ADDIE | Analysis, Design, Development, Implementation and Evaluation |
| BHL | Behavioral Health Laboratory |
| CDA | Career Development Award |
| COIN | Center of Intervention |
| CREATE | Collaborative Research to Enhance and Advance Transformation and Excellence |
| CFI | Comparative Fix Index |
| COVID | Corona Virus Disease |
| CDW | Corporate Data Warehouse |
| CHOICE | Choosing Healthier Drinking Options in Primary Care |
| DSM-5 | Diagnostic and Statistician Manual of Mental Disorders-Fifth Edition |
| DO-MoST | Drinking Options: Motivate, Shared Decisions, Telemonitor |
| GEE | Generalized Estimation Equations |
| GLM | General Linear Mixed Model |
| HSR&D | Health Services Research and Development |
| HIV | Human Immunodeficiency Virus |
| IIR | Investigator Initiated Research |
| MOCA | Montreal Cognitive Assessment |
| MI | Motivational Interviewing |
| NIAAA | National Institutes on Alcohol Abuse and Alcoholism |
| non-AUD | non-Alcohol Use Disorder |
| non-VA | non-Veteran Administration |
| non-VHA | Non-Veteran Health Administration |
| PHQ-2 | Patient Health Questionnaire – 2 items |
| PHQ-9 | Patient Health Questionnaire – 9 items |
| PTSD | Post-Traumatic Stress Disorder |
| PCL-5 | PTSD Checklist for DSM-5 |
| PC | Primary Care |
| PC-MHI | Primary Care-Mental Health Integration |
| PCPs | Primary Care Physicians |
| PC-PTSD | Primary Care-Post-Traumatic Stress Disorder |
| PI | Principal Investigator |
| QUERI | Quality Enhancement Research Initiative |
| RCT | Randomized Controlled Trial |
| RRP | Rapid Response Project |
| RMSEA | Root Mean Square Error of Approximation |
| South Central MIRECC | South Central Mental Illness Research, Education and Clinical Center |
| SRMSR | Standardized Root Mean Square Residual |
| SLAC | Strengths-based Linkages to Alcohol Care |
| SUD | Substance Use Disorder |

| | |
|---|---|
| SUMMIT | Substance Use Motivation and Medication Integrated Treatment |
| TLFB | Timeline Follow-Back |
| UC | Usual Care |
| VACO | VA Central Office |
| VA/DoD | Veterans Administration/Department of Defense |
| VA HSR&D | Veteran Administration Health Services Research and Development |
| VHA | Veterans Health Administration |
| VHA PC | Veteran Health Administration Primary Care |
| VHA PCP | Veteran Health Administration Primary Care Physician |

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## Protocol Title: Multi-site Pilot Trial of Strengths-based Linkage to Alcohol Care ((C2C)) – Aim 2

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Data collection will occur at two sites: Little Rock, AR and Palo Alto, CA

## 2.0 Introduction

Annually, 10% of Veterans in VHA primary care (PC) screen positive for hazardous drinking, which ranges from drinking above low-risk drinking limits to meeting diagnostic criteria for an alcohol use disorder (AUD),[3] with a higher prevalence (23%) found in younger (age ≤ 30) Veterans.[1] Further, 27% of Veterans screening positive for hazardous drinking have an AUD.[2] Of Veterans with hazardous drinking, rates of comorbid PTSD and depression are high (25% and 38%, respectively).[124] Veterans with PTSD who engage in hazardous drinking are at high risk for developing more severe drinking problems and depression when compared to those who drink and do not have PTSD.[4,6] And Veterans with PTSD or depression are four times as likely to report hazardous drinking as Veterans without either of these disorders.[7] To minimize adverse outcomes, it is essential for Veterans screening positive for hazardous drinking and PTSD and/or depression (A-MH) to link to evidence-based alcohol care (behavioral and medication-assisted treatments, mutual-help, and e-health, collectively henceforth referred to as "alcohol care").

Currently, two options exist for linking Veterans with A-MH in VHA PC to alcohol care, neither of which is effective. First, PC providers can directly refer hazardous drinkers to specialty substance use disorder (SUD) care.[8] However, only 12% (18% with AUD) of Veterans screening positive for hazardous drinking receive specialty SUD care within one year following screening.[125] Although not all Veterans with a positive alcohol screen require referral to specialty SUD care, many do, especially those with evidence of mental health comorbidities.[8] Second, in FY 2007, VHA implemented Primary Care-Mental Health Integration (PC-MHI; mental health providers co-located in the PC setting) nationwide, partly to improve access and linkage to care for substance use.[10] However, only 4% of PC-MHI provider-patient encounters nationwide are alcohol-related,[11] suggesting few Veterans with hazardous drinking are seen by a PC-MHI provider (e.g., psychologist, social worker). These findings indicate that existing VHA options for linking Veterans with A-MH in PC to alcohol care are not effective. Further, low motivation to seek care, due to lack of knowledge about available care options, and uncertainty about which option to choose, are important obstacles to pursuing alcohol care among hazardous drinking Veterans.[67] We have identified an intervention, Strengths-based Linkage to Alcohol Care ((C2C)),[12] that can help overcome these obstacles. (C2C) increases motivation to pursue alcohol care, understanding of available care options, and certainty about which care option to pursue by (1) identifying patient strengths to facilitate care linkage, (2) encouraging collaborative decision-making using a menu (**Appendix A**) of evidence-based care options, (3) identifying barriers to care and how to resolve them, and (4) continuously monitoring progress toward care linkage.[12,13,15](C2C) has been shown to be effective in linking civilians with substance use[12,15] and chronic mental health and medical conditions[13] to care. However, it has not been studied in the VHA or with Veterans engaging in hazardous drinking who have mental health co-morbidities. For this reason, obtaining preliminary evidence for its acceptability and efficacy in this population, are high priorities for our operations partners.

## 3.0 Objectives

This study has two aims:

**Aim 1:** To adapt (C2C) for use among *Veterans with A-MH* and for delivery by telephone in the VHA PC setting. We will conduct qualitative interviews/focus groups with three participant groups: 1) Veterans, 2) PC staff, and 3) VA operational partners to ensure that the content and format of (C2C) are adapted so they are relevant and acceptable to these stakeholders.
*Aim 1 received IRB approval and is ongoing.* **We are requesting approval for Aim 2**

**Aim 2:** To determine (a) the feasibility of conducting a larger scale randomized controlled trial (RCT) to test (C2C)'s effectiveness and (b) (C2C)'s acceptability among *Veterans with A-MH in PC*, and to explore (c) the efficacy of (C2C) in *this Veteran population*. To achieve Aim 2, we will conduct a multi-site pilot RCT of (C2C) at two VA medical facilities (Little Rock, AR and Palo Alto, CA). In addition to assessing the feasibility (e.g., rates of enrollment and follow-up, fidelity to the (C2C) intervention) of conducting a subsequent larger RCT and (C2C)'s acceptability ((C2C) completion rates, satisfaction with (C2C)) among Veterans (2a-2b), we will explore the impact of (C2C) on Veterans' linkage to and *utilization of* alcohol care, and their alcohol and mental health outcomes, at 3-month follow-up (2c). We will also, at 3-month follow-up, conduct debriefing interviews with 20 participants assigned to the (C2C) condition to obtain data on its feasibility, acceptability, and perceived efficacy

The proposed aims address a critically important gap in Veterans' health care - specifically, the need to identify effective strategies for linking Veterans in VHA PC who have a positive screen for *A-MH* to alcohol care. Our VHA operations partners (including Drs. Edward Post, National Primary Care Director for Primary Care-Mental Health Integration and Andrew Pomerantz, Mental Health Director for Integrated Services) in the Office of Primary Care and Office of Mental Health and Suicide Prevention are highly interested in implementing (C2C) in VHA PC should it be found effective in a subsequent, fully powered RCT. This proposal directly supports a recent recommendation by the National Academies to improve VHA transitional services by helping Veterans to better access substance use care.[14] The aims of this proposal also support VA HSR&D priorities (Access to Care, Mental Health, and Primary Care) by adapting and pilot testing a novel intervention to help facilitate Veterans' linkage to alcohol care. Increasing the use of alcohol care in this high need Veteran population is likely to lead to significant reductions in acute health care costs[106] as well as improved outcomes.[107]

## 4.0 Resources and Personnel

***Michael A. Cucciare, PhD**, **Principal Investigator**. Dr. Cucciare is a Senior Research Health Scientist at the VA HSR&D COIN Center for Mental Healthcare and Outcomes Research (Little Rock) and Associate Director for Research Training at the South-Central Mental Illness Research, Education and Clinical Center. He is also an Associate Professor (with tenure) and Associate Director of the Center for Health Services Research in the Department of Psychiatry at UAMS. He is Co-Associate Director of the NIDA T32 Addiction Training Program at UAMS. He is a past recipient of a VA HSR&D Career Development Award - 2 (CDA-2) and a Licensed Clinical Psychologist with expertise in treating Veterans and civilians with substance use disorders. He has over a decade of experience treating

Veterans and civilians with substance use disorders, including those with mental health comorbidities. He has served as principal investigator (PI) and co-investigator (Co-I) on several large, VA HSR&D-funded projects focused on implementing and evaluating interventions for treating hazardous drinking in medical settings (CRE 12-009; CDA 08-004), reducing benzodiazepine use in Veterans in primary care (IIR 18-026), and implementing computer-delivered interventions for treating Veterans with anxiety disorders, PTSD and depression in VA community-based outpatient clinics (CRE 12- 314). His background in treating persons with substance use disorders, adapting and testing interventions for treating substance use and comorbid mental health disorders, clinical trials methodology, and using technology to deliver evidence-based mental health practices in primary care make him well-suited to serve as PI on this project. Dr. Cucciare will share (with Dr. Humphreys) responsibility for all aspects of the study including development of study procedures, research methods, and policies; and adaptation of the intervention ((C2C)) to VHA primary care. He will lead the study team in Little Rock and co-lead staff training at both sites; ensure all regulatory permissions to conduct the project are received; and share responsibility with Dr. Humphreys in writing of reports, manuscripts, and disseminating study findings to HSR&D, VACO partners, and primary care staff at both sites, and writing of scientific publications.

**Keith Humphreys, PhD, Principal Investigator.** Dr. Humphreys is an HSR&D Senior Career Research Scientist in the Palo Alto VA.. Dr. Humphreys is an internationally recognized scientist in the area of substance use disorders with extensive VA operations experience and has been appointed by multiple VA secretaries and undersecretaries of health to help implement evidence-based care of Veterans. As one of the two PIs of this study, Dr. Humphreys will share the responsibility of leading the study with Dr. Cucciare. He will supervise the research assistant at the Palo Alto site; co-lead management of the overall study and training and fidelity monitoring of the Linkage Coordinator; be responsible for keeping the study on track in terms of recruitment and follow-up rates; and implement best practices for ensuring participant retention and high follow-up rates. Dr. Humphreys will co-lead study meetings, and work with Dr. Cucciare to complete all regulatory and reporting requirements, and ensure that VACO partners (e.g., Drs. Post and Pomerantz) are updated regularly with regard to study progress. He will also assist in manuscript development and efforts to disseminate study results to VACO partners.

**Christine Timko, PhD**, **Co-Investigator**. Dr. Timko is a Senior Research Career Scientist, and Associate Director, at the HSR&D Center for Innovation to Implementation at the Veterans Affairs Palo Alto Healthcare System.. She has conducted health services research focused on patients with addiction, other mental health disorders, and co-occurring conditions for 33 years and published extensively in these areas. Dr. Timko will provide consultation on strategies for recruitment and interpretation of treatment outcome data.

**Ronald Thompson, PhD**, **Co-Investigator**. Dr. Thompson will provide expertise for adapting the (C2C) intervention for use in VHA primary care and train the Linkage Coordinator to implement the intervention, adapting existing materials to monitor fidelity of intervention delivery, monitoring intervention delivery to ensure fidelity, analyzing/interpreting data, and preparing manuscripts. Dr. Thompson has an MSW and PhD in Social Work and has instructed graduate students in strengths-based treatment approaches for 30 years. He has been the principal investigator of two large NIH-funded studies (R21AA017862; K23DA032323) designed to develop and test the feasibility and preliminary effectiveness of brief motivational interventions to reduce substance use and

sexual risk behaviors among homeless young adults, a highly vulnerable and under-researched population. He successfully administered these projects (e.g., staffing, training, intervention development/adaptation, fidelity of intervention delivery, research protections, budget) and effectively collaborated with co-investigators, research staff, and study sites. Dr. Thompson is a Licensed Certified Social Worker and able to clinically manage crisis situations and adverse events that might occur.

**Xiaotong Han, MS**, **Co-Investigator**. Ms. Han has worked as a data analyst for the HSR&D COIN in Little Rock, South Central MIRECC, and Center for Health Services Research at UAMS for over 15 years and has played a major role in Drs. Cucciare's and Humphreys' funded studies and publications. She will participate in meetings to review instruments and begin setting up databases. She will receive databases from the research assistants on a regular basis, help with data cleaning and management, and will conduct quantitative data analyses for publications and presentations.

**Edward Post, MD, Co-Investigator.** Dr. Post is the National Primary Care-Mental Health Integration director for the VA. He is one of our core VACO partners for this project. Dr. Post has made significant contributions in developing the study aims and conceptualizing the implications of the study for national PC-MHI practice and policy and is committed to rolling out (C2C) nationally should it be found to be effective. Dr. Post will also provide expert consultation on the interpretation of data from both aims, manuscript development, and, if justified, will contribute to a subsequent IIR proposal to conduct a fully powered RCT of (C2C) in VHA primary care.

***Kathy Marchant, RN, Project Coordinator.** Ms. Marchant will be responsible for overall day-to-day management of the project. She will work closely with the PIs and research assistants at the two sites to coordinate research efforts, ensure timelines are met, and assist with regulatory requirements. She will also co-lead study meetings, help with scheduling and conducting interviews/focus groups, and interpreting data.

***Deanna Hildebrand, RN, Project Coordinator.** Ms. Hildebrand will work closely with Ms. Marchant assisting with the overall day-to-day management of the project. She will work closely with the PIs and research assistants at the two sites coordinating research efforts, project management to include regulatory maintenance. She will assist with the recruitment, enrollment, Veteran assessments, and debriefing interviews/focus groups at both sites.

***Penny White, BS, Research Assistant.** Ms. White will develop the assessment database in Microsoft Access, contact and screen Veterans for eligibility, and conduct informed consent. She will also conduct 3-month follow-up assessments, input data, and help with data cleaning to prepare the database for statistical analysis. She will assist in debriefing interviews/focus groups at both sites, participate in study meetings; coordinate meetings between the two study sites; and develop documents to be used between the study sites to ensure standardization of study materials.

***James (Silas) Williams, MS, Programmer**. Mr. Williams is a programmer at the HSR&D COIN in Little Rock. He will be responsible for obtaining CDW data pertaining to eligible patient participants at the study sites. He will obtain data regularly on potential participants, clean the data, and provide lists of potential participants to the two sites. He will assist in the development of the Access database used to conduct all telephone baseline and follow-up interviews/focus groups, conduct data entry and cleaning, and

assist the team in developing a database to be used in analyses conducted by Ms. Han.

***Sharfun Ghaus, MD, Research Assistant.** Dr. Ghaus will complete eligibility screenings and obtain consent for both study aims; conduct qualitative interviews/focus groups; help with qualitative data analysis; conduct baseline and follow-up assessments; participate in study meetings; complete debriefing interviews/focus groups; assist (with help from Ms. White) in coordinating meetings between the two study sites; co-develop documents to be used between the study sites to ensure standardization of study materials; and enter data. She is experienced in these tasks through her work on another multisite study led by Drs. Humphreys and Cucciare (on family and friends of Veterans and civilians in addiction treatment).

***Cristy Benton, LCMSW, (C2C) Coach.** Ms. Benton is a Licensed Certified Social Worker who has experience providing evidence-based mental health interventions to patients with substance use disorders. She will receive training in (C2C) from Drs. Cucciare and Thompson and participate in fidelity monitoring. She will conduct (C2C) sessions with Veterans randomized to the (C2C) condition; help with scheduling and rescheduling (C2C) intervention sessions, track number of sessions attended by participants, and document barriers to delivering (C2C); assist with completing baseline and follow-up assessments (*only with participants assigned to the control condition to limit reactivity to her by Veterans assigned to the (C2C) condition, thus preventing bias to self-report data*). She will participate in ongoing (C2C) supervision; help with data entry and management; participate in study meetings; and assist with IRB and other regulatory requirements.

*Identifies those individuals who will have access to individually identifiable data via data from interviews, intervention delivery or from the CDW.

# 5.0 Study Procedures

## 5.1 Study Design

To achieve Aim 2, we will conduct a multi-site pilot RCT of (C2C) at the Little Rock and Palo Alto VA medical facilities. **Aim 2a**: To assess the feasibility of conducting a full-scale trial of (C2C)'s effectiveness, we will determine the proportion of Veterans screening eligible for the study who enroll, number of Veterans enrolled per month, participant follow-up rates, and Linkage Coordinator fidelity to the (C2C) intervention. **Aim 2b:** To assess (C2C)'s acceptability, we will determine the percentage of Veterans completing at least 3 sessions of (C2C) (> 3 sessions are associated with higher rates of linkage), percentage completing all 5 sessions of (C2C), and Veteran satisfaction with the (C2C) intervention. **Aim 2c:** We will explore the efficacy of (C2C) to improve Veterans' linkage to and utilization of alcohol care as well as their alcohol and mental health (PTSD, depression) outcomes, at 3-month follow-up. A 3-month follow-up has been used in prior research with civilian substance users and will allow for direct comparison of results.

We will recruit 140 Veterans (70 at each site) who screen positive for A-MH. To be eligible, participants will have screened positive for hazardous drinking in PC and have a positive screen for PTSD and/or depression in PC or other VA clinic (e.g., outpatient mental health or emergency department) within the past year. Participants will be recruited via the VA CDW (see Section 5.3 for details). During study recruitment, all eligible PC patients will receive usual care (UC). UC includes a structured clinical reminder to the provider to facilitate brief alcohol counseling (usually performed the same day as screening) and an offer of further specialized assistance to Veterans meeting VA criteria for referral. Both sites

will recruit potential participants. Potential participants will be mailed a letter inviting them to participate in the study. Veterans interested in learning more about the study will be connected with the research team who will confirm eligibility of interested Veterans by rescreening for hazardous drinking, and PTSD or depression (*to determine if they continue to meet criteria*) and for eligibility criteria that could not be prescreened with CDW data such as cognitive function, no past-90-day AUD treatment or weekly mutual-help, access to phone, available contact, non-participation in Aim 1. Eligible Veterans who consent to participate will be randomly assigned to the UC or (C2C) conditions using the Research Randomizer website.

UC. All participants will receive UC delivered by their VHA PCP that includes mandated brief counseling and referral to specialty SUD care per VA guidance. We chose existing UC as the control condition (rather than a filler condition equating for time and attention) for two reasons. First, before deciding whether to implement (C2C) widely in VA, our partners want to know whether (C2C) offers any benefit over UC as UC is actually practiced, rather than a control condition that they would not consider implementing.[143,144] Second, having UC as the control condition will facilitate comparisons of outcomes from this study (and a future full-scale RCT) with those from RCTs of linkage interventions delivered in PC that aimed to improve care use and outcomes.[126,127]

(C2C). Veterans assigned to the (C2C) condition will receive UC plus the (C2C) intervention. They will be contacted by the study Linkage Coach by phone to schedule their first session. The (C2C) protocol (Appendix D) will provide up to five telephone or virtual sessions over 7 weeks. Sessions will last about 30 minutes, depending on the participant's specific needs. In our current research with friends and family of patients in SUD treatment (*NIAAA R01AA024136: PIs Timko and Cucciare*), we are finding that telephone linkage intervention sessions rarely last longer than 30 minutes. Both project sites can provide the types of alcohol care that (C2C) will offer including addiction outpatient and residential specialty care offering behavioral therapies, pharmacotherapy, and 12-step Intervention. (C2C) sessions will be offered virtually or by telephone giving participants a choice (as was recommended during Aim 1 focus groups with stakeholders. Veterans prefer choice in how care is delivered.

Research assistants, blinded to condition, will collect baseline and follow-up data (3-month post randomization) from participants via telephone. Study staff may also communicate with Veterans via text messaging after initial contact has been made. Ie: for scheduling purposes such as potential appointment dates/times to discuss study and or complete assessments only. Text messages will be sent by VA research staff from VA issued (government furnished equipment (GFE) cell phones. Based on prior studies, each assessment will take about 1 hour. If participants tire, assessments will be broken into multiple segments. We will use an intent-to-treat design and follow participants who do not complete the intervention. Participants will be compensated $25 and $30 for completing the baseline and 3-month follow-up assessments, respectively.

To ensure high follow-up rates, we will adhere to well-established procedures for locating and following participants with substance use and mental health disorders in longitudinal studies. We have been successful in retaining research participants through proactive retention strategies, tracking protocols, and interviewer training. Our retention strategies include: using interviewers who are comfortable with the study population and trained to establish rapport; maintaining toll-free telephone numbers for participants to report contact information changes; obtaining and verifying in-depth locator and tracking information at baseline, and updating records at each interview and between interviews; maintaining consistent contact between interviews (e.g., thank you cards to enhance rapport and verify addresses), and keeping detailed records of contact attempts.

In addition, at 3-month follow-up, we will conduct telephone or virtual debriefing

interviews with 20 participants assigned to the (C2C) condition to obtain data on its feasibility, acceptability, and perceived efficacy (including reasons participants think (C2C) is/is not helpful; see Appendix G). Interviews will be audiotaped and transcribed to facilitate qualitative data analysis. Participants will be compensated $25 for the completion of the interview. Veterans who fail to receive 3 (C2C) sessions (n = 14; 7 at each site; receiving > 3 sessions is associated with linking to care) and Veterans who receive 3 or more sessions (n = 6; 3 at each site) will be interviewed at the completion of their 3-month follow-up. Interviewing these subgroups will allow for more interviews with Veterans who did not receive a likely effective "dose" of (C2C) while also learning from Veterans who successfully completed the intervention. In both subgroups, we will ensure that Veterans with probable AUD, probable PTSD, and at least moderate depression will be represented. Interviews will identify aspects of (C2C) Veterans found helpful/not helpful for linking to alcohol care and potential suggestions for improvement. Findings may inform strategies for deterring (C2C) drop out and improving (C2C) use and completion. Findings will also further inform conceptual model development (e.g., identification of other potential mechanisms) of (C2C) to be tested in a subsequent RCT.

We do not anticipate any significant risks associated with study participation; however, there is the possibility that Veterans' will experience some emotional discomfort while discussing their alcohol use or mental health symptoms or in thinking about their care experiences or preferences. Every effort will be made by the interviewer to reduce potential risks including frequently pausing or discontinuing the interview (depending on the preference of the interviewee), should a participant express concern and/or demonstrate nonverbal evidence of discomfort while participating in the interview.

Participants will be told that they may withdraw from the project at any time and refrain from answering specific questions, that all information will be confidential and used only for project purposes, and that they can contact the principal investigators (Drs. Cucciare and Humphreys) or RAs with any questions at any time. When attempting to contact potential or enrolled participants, should someone other than the participant answers the telephone, study staff will simply state that he or she is trying to locate the individual regarding a health services survey. The project will not be described in detail to any non-participant by study staff as a study involving alcohol use. All contacts and interviews will be conducted in a manner that protects the dignity of participants.

Study staff will be trained in how to respond should a participant express the need for help with a personal or emotional problem (e.g., depression, suicidal crisis). Dr. Cucciare has extensive experience in conducting such training and his research staff is well-versed in what to do should situations like this arise. Should a participant express suicidal or homicidal ideation, or other serious psychiatric or medical symptoms, research staff will remain on the phone with participant with warm hand-off to VA crisis line, PI or other appropriate service. Dr. Cucciare will be notified immediately. Dr. Cucciare is a licensed clinical psychologist who will be responsible for oversight of all unexpected/unanticipated events and will be available to speak with the participant and/or consult with research staff to ensure the participant is connected with the appropriate services. Additional on-site licensed psychologists (e.g., CAVHS's Little Rock COIN has > 5 licensed psychologists) as well as Dr. Thompson and Ms. Benton (both licensed social workers) will act as back-up contacts if Dr. Cucciare is not immediately available. After any participant's expression of severe distress, project staff will make all reasonable attempts to re-contact the participant to monitor his or her well-being until the acute situation is resolved.

## 5.2 Recruitment Methods

We plan to recruit 140 Veterans. Of those 140, we plan to conduct 20 debriefing interviews (from the 140 Veterans recruited) with participants who received the (C2C) intervention at the 3-month follow-up.

To recruit Veterans from both study sites for the RCT (N=140, 70 from each site) we will use the VA Corporate Data Warehouse (CDW) to identify potentially eligible Veterans seen in PC at each of the two sites. We will have to consent/enroll approximately 150 Veterans (more than we initially estimated) from each site prior to recruitment due to screening requirements by our local IRB. We are required to consent prior to screening eligibility. Therefore, there will be participants initially consented/enrolled that will not meet study eligibility. We will identify Veterans using the following criteria:
(1) an AUDIT-C score of $\geq$ 5 (used by VHA to indicate hazardous drinking) within the PC setting and (2) a positive screen for PTSD (Primary Care PTSD Screen for DSM-V [PC-PTSD-5] score of $\geq$ 3 and/or depression (Patient Health Questionnaire-2 score of $\geq$ 3)
(3) during a VHA PC or other VHA clinic visit within the past year and invite them to participate in the study.
Data will be collected on potential participants for both study sites. That is, we will generate a list of Veterans from the Little Rock VA and Palo Alto VA to invite to participate. Little Rock will be responsible for generating that list of Veterans. We will then securely share the list of Veterans identified at the Palo Alto VA with the Palo Alto study team. Each site will invite their own list of Veterans to participate and complete screening, consenting the baseline interview. Both sites will randomly select a subsample of Veterans from the CDW dataset to whom we will mail invitation opt-out letters and a study information sheet prior to contacting Veterans by phone. There will be no study-specific information on the envelopes exterior that we mail to the Veterans that could potentially link the participant to the individual research project. To ensure inclusion of women, we will invite all women identified in the CDW dataset to participate in the study at the two sites. We expect women will represent about 3%-10% of the identified Veterans. We have learned from our prior work that study participation is maximized when potential participants receive a study packet that includes an invitation letter to include information on how to opt-out (should they not wish to be contacted) and notification that we will contact them by telephone approximately 10 days following the mailing. Veterans who opt-out will not be contacted and listed in a No-Contact protocol. Those who do not opt-out will be contacted by telephone 10 days after the initial mailing. Study staff may attempt to contact Veterans via text messaging, but only after initial contact has been made.The Veteran will be asked to have the information sheet in front of them for the discussion. The study will be presented to potential participants as research to learn more about VA and community resources to improve their health. Study staff will review the study informed consent script with potential participants, explaining that during a recent health care visit they answered questions about their alcohol use in a way that indicated possible difficulties around drinking.
At the time study staff are in contact with Veterans about participating (e.g., Veterans contact the study team or study team contact them via follow-up phone call), research assistants (RAs) will obtain Veteran consent to participate and confirm continued eligibility criterion for hazardous drinking by administering screeners (AUDIT-C; score > 5), PTSD (PC-PTSD-5; score > 3), and/or depression (PHQ-2; score > 3). RAs will also assess cognitive functioning using the Montreal Cognitive Assessment (MOCA) section on Orientation. Veterans not able to answer the Orientation items (date, month, year, day of the week) with reasonable accuracy (e.g., the month indicates the wrong season; year is incorrect) and whose interview suggests likely cognitive impairment (e.g., difficulty understanding questions and following the conversation) will be ineligible to participate as they are likely to be too impaired to provide fully informed consent and/or understand study procedures. Research assistants will review study processes, procedures, risks and benefits and answer questions about study participation.
Participants will be compensated $25 and $30 for completing the baseline and 3-month follow-

up assessments, respectively. Veterans will be compensated in the form of a check from the Department of Treasury. Research assistants at the two sites (Palo Alto, CA and Little Rock, AR) will be responsible for ensuring Veterans receive compensation for their study participation.

**For the debriefing interviews**, we will recruit 20 Veterans from the intervention group at the 3-month follow-up period. Veterans who fail to receive 3 (C2C) sessions (n = 14; 7 at each site; receiving ≥ 3 sessions is associated with linking to care)[12] and Veterans who receive 3 or more sessions (n = 6; 3 at each site). At the time of 3-month follow-up, we will randomly select 20 participants from the intervention arm and invite them to participate in a debriefing interview that will occur immediately after completing their 3-month follow-up assessment. If they agree, they will be interviewed at the completion of their 3-month follow-up (*see Appendix G for a draft interview guide*). This interview, which will be recorded, is expected to last 30-60 minutes. Participants will be compensated an additional $25 for their participation in this interview.

## 5.3 Informed Consent Procedures

We are requesting a waiver of documentation of informed consent as the informed consent process will be conducted over the telephone and the intervention will be delivered virtually or by telephone. Informed consent will be obtained by IRB approved study staff who have been trained and are experienced in consenting Veterans for intervention studies within VHA. Veterans will be asked to provide consent to participate in part 1 (RCT) and part 2 (debriefing interviews). We will inform the Veteran that they may also be asked to participate in an additional interview (part 2) which will be an interview to provide feedback on their study experience. Veterans will be encouraged to ask questions about study participation at any time during the study. We will keep an electronic record (e.g., excel sheet) of Veterans who agree to participate. Consent will be obtained by research trained and IRB approved research staff to include Deanna Hildebrand, RN, Kathy Marchant, RN, Sharfun Ghaus, MD, Penny White, BS and Cristy Benton, MSW.

## 5.4 Inclusion/Exclusion Criteria

To be eligible for Aim 2, Veterans (N = 140) will
(1) have screened positive for hazardous drinking (AUDIT-C score > 5) and
(2) PTSD (PC-PTSD-5 score > 3) and/or depression (PHQ-2 score > 3) in the prior 12 months and have positive rescreens
(3) not have received specialty SUD treatment or participated in weekly mutual-help groups in the past 90-days
(4) not have significant cognitive impairment
(5) have ongoing access to a mobile or landline telephone
(6) not have participated in an interview for Aim 1

## 5.5 Study Evaluations

(C2C) fidelity. To assess the integrity of the (C2C) intervention throughout the study, Dr. Thompson and the PIs will complete the (C2C) Fidelity Assessment (Appendix E), consisting of a checklist of core (C2C) components, after the first 10 phone calls (and 4 randomly chosen phone calls per month thereafter) between the Linkage Coordinator and participants. The Linkage Coach will audio-record all sessions (with verbal informed consent). This will allow selected sessions to be evaluated for fidelity. Corrective feedback will be provided to the

Linkage Coach if needed. We have had no problems with adherence or appropriate response to feedback in our previous or ongoing studies. In addition, to facilitate future implementation of (C2C), on an ongoing basis, the Linkage Coordinator will document any barriers or facilitators to delivering the intervention that arise over the course of the study weekly via an electronic facilitation log.

Outcomes and measures. Feasibility outcomes are: **(a)** the proportion of Veterans screening eligible for the study who enroll, **(b)** monthly enrollment rates compared to our benchmark of *at least 10* Veterans per month (the estimated enrollment rate needed for a full scale RCT), **(c)** participant 3-month follow-up rates compared to a benchmark of ≥ 75%; and **(d)** (C2C) fidelity as rated by Dr. Thompson and the PIs using the (C2C) Fidelity Assessment. A rating of 80% completion of the basic core elements of (C2C) will be used to define fidelity. These measures will help us assess the number of eligible Veterans we need to screen to meet our target enrollment (overall, monthly) for a full-scale RCT, the effectiveness of retention methods, and our ability to train project staff to administer (C2C) with fidelity.

Acceptability will be operationalized as (a) the percentage of Veterans randomized to (C2C) who complete at least three sessions and all five sessions (a positive outcome will be defined as ≥ 50% of Veterans meeting each criterion), and (b) Veterans' satisfaction with (C2C), assessed with the VA Multisite Study's measure of satisfaction with SUD treatment (e.g., the extent to which (C2C) met the Veteran's needs). A successful outcome will be defined as a summary score ≥ 17. These data will help determine whether further modifications to (C2C) are needed prior to a subsequent RCT to improve Veterans' (C2C) attendance and/or to increase (C2C)'s perceived value in this population.

To explore (C2C)'s efficacy*,* we will collect the following data at baseline and 3-month follow-up (exceptions are noted below). These data will be collected via paper and pencil assessment or REDCap.

Demographics: age, sex, gender, race/ethnicity (baseline only), employment, income, and housing.

Alcohol care preferences will be assessed using a single-item question ("Among the following options [we will list each option available], what type*(s)* of alcohol care or help do you prefer at this time?"). *Participants may choose more than one option and/or change their preference at any time.*

Alcohol consumption (quantity/frequency), depression, and PTSD**.** Alcohol quantity and frequency will be measured using the 90-day Timeline Follow-Back instrument (TLFB). The TLFB is a calendar-based, retrospective self-report measure that assesses quantity/frequency of alcohol consumed over a specified period of time. It is reliable and accurate when administered over the telephone. We will use TLFB data to calculate percent of drinking days and percent of heavy drinking days (≥4 standard drinks per day for women; ≥5 for men). *We will use the Patient Health Questionnaire-9 (PHQ-9)[79] and PTSD Checklist-5 (PCL-5)[119] to measure depression and PTSD symptoms, respectively.*

AUD diagnosis and severity will be measured using the 11 items in the DSM-5.[80]

Drug use will be measured using the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[82] to assess lifetime (baseline only) and past 90-day drug use. The ASSIST assesses use of illicit drugs (stimulants, inhalants, street opioids) and non-medical use of prescription drugs (opioids, sedatives).

Overall health will be measured using a single item to assess general health.

Strengths and barriers to recovery will be assessed with 32 items assessment measuring strengths (e.g., plan for the future, volunteer) and barriers (e.g., smoking, bad debts) to substance use recovery.

eHealth literacy will be assessed with an 8-item assessment of internet health literacy.

Substance use and mental health care utilization. We will use an adapted version of the Addiction Severity Index (ASI)[83] to assess the participant's VA and non-VA history of lifetime

alcohol/drug treatment, and mental health care use (baseline only). Data on non-VA health services use will be collected at baseline and follow-ups to help determine whether the two study arms are balanced.

At 3-month follow-up, we will use the TLFB method (as used in Dr. Timko's current DO-MoST trial, IIR 15-298) to assess participants' self-reported prior 90-day use of VHA and non-VHA alcohol care and determine the primary efficacy outcomes: linkage to and utilization of alcohol care. Linkage to alcohol care is a dichotomous variable (yes/no), with "yes" defined as the participant reporting at least one of the following[12]: a) attended an initial meeting with an outpatient (PC-MHI, specialty care) or residential program; **b)** attended a mutual-help group meeting; received > 30-days' supply of AUD medication;[126] or **c)** went online to access e-health for alcohol information.[145] Utilization of alcohol care will be defined using two methods. Following Dr. Timko's current DO-MoST trial (IIR 15-298), we will define utilization as the percentage of days, in the past 90-days, that participants obtained any alcohol care. In addition, following the method used in the CHOICE trial,[126] we will measure the total number of alcohol care options participants obtained over the past 90-days; scores will range from 0 (no care) to 4 (obtained all types of care: outpatient/residential, mutual-help, medication (>30-days' supply), e-health).

We will also obtain data from the CDW to identify use of VA substance use and mental health care (including care received in PC-MHI), including entry into addiction treatment, type of care/setting, and frequency/duration of each care type at follow-up. Secondary efficacy outcomes are alcohol consumption (quantity/frequency), depression, and PTSD symptoms. They will be measured by the 90-day TLFB, PHQ-9, and PCL-5, respectively. At follow-up, participants in the (C2C) condition will receive the VA Multisite Study's measure of satisfaction with SUD treatment.[96] Mediators. We will collect data at baseline and at follow-up on proposed mediators (see Figure 1). Motivation to seek care will be assessed with the Readiness Ruler.[84] This instrument asks participants about their motivation to seek alcohol care, on a scale of 1 (less – not ready) to 10 (more – trying to seek care). Decisional conflict will be assessed with the Decisional Conflict Scale, a self-report measure used to assess decision certainty and comfort.[85,86] The scale's 16 items yield five subscales (Informed, Values Clarity, Support, Uncertainty, Effective Decision) and a total score.

## 5.6 Data Analysis

Aim 2 analysis plan (explore (C2C)'s efficacy). We will check data for errors or inconsistencies. We expect little missing data; however, will use multiple imputations if the amount of missing data is large and random, and Bayesian methods if missing data is not at random. We will examine all continuous outcomes for normality using visual inspection or appropriate statistical tests. We will evaluate whether the two conditions differ at baseline on demographic, clinical, and health care utilization characteristics. For continuous variables, we will use an independent t-test or nonparametric Wilcoxon test; for categorical variables, we will use a chi-square independence test. Variables associated with the condition will be included in our models as covariates. For outcomes with a normal distribution, we will use generalized estimating equations (GEE)[146] or general linear mixed (GLM) models[147,148] to account for correlations within participants over time. For variables that are non-normally distributed, we will identify appropriate distributions along with corresponding links and use GEE or generalized linear mixed (GLM) models to account for correlations within participants over time. The interaction between condition and time will be included in all models.

The proposed pilot RCT is not powered to test efficacy, mediator, and moderator hypotheses. We will therefore explore the efficacy of (C2C) by comparing the two conditions on the primary outcomes of linkage to and utilization of alcohol care, and secondary outcomes of alcohol use, depression, and PTSD symptoms. To explore alcohol care linkage (initial contact

with a provider/source of help; yes or no), we will employ GEE or GLM models using binomial distribution with logit link to determine whether Veterans differ, by condition, on linkage at 3-month follow-up. To explore the utilization of alcohol care (total number of alcohol care options obtained in the past 90-days) we will use GEE or GLM models with cumulative logit or generalized logit to determine whether Veterans in the (C2C) condition had increased utilization of alcohol care relative to UC over time. We will include a binary variable for study condition ((C2C) vs UC) and time for each interview in the regression models and an interaction term between these two variables. To explore the utilization outcome of percentage of days in the past 90-days alcohol care was obtained, we will use the analytic approach described below for the alcohol use outcome. We will include study site in the regression models along with any other variables that are significantly associated ($p<.05$) with condition at baseline. The analyses for alcohol (percent of drinking days and heavy drinking days), PTSD, and depression outcomes will be performed using GEE or GLM models to examine the effect of (C2C) over time. Normal distribution will be specified if an outcome is normally distributed. Otherwise, an appropriate distribution (e.g., beta distribution for alcohol outcomes with percentages; gamma distribution for PTSD and depression outcomes) will be identified with the corresponding link specified. Variables for condition, time, site, and covariates will be included in all of the models along with the interaction term between condition and time. Models will be developed for each outcome separately.

Explore mechanisms (reasons (C2C) is effective). Decisional conflict and motivation to seek alcohol care will be explored as potential mediators between condition and outcomes. We will conduct analyses using structural equation modeling (controlling for covariates) that correspond to a hypothesized causal sequence among (1) (C2C), (2) less decisional conflict and more motivation to seek alcohol care, (3) linkage to/utilization of alcohol care, and (4) alcohol, PTSD, and depression outcomes (Figure 1).[121] We will include the following paths simultaneously in the model: (1) condition ((C2C) vs. UC) to decisional conflict and motivation to seek alcohol care, (2) decisional conflict and motivation to seek alcohol care to linkage to/utilization of alcohol care, and (3) linkage to/utilization of alcohol care to alcohol, PTSD, and depression outcomes. The dummy variables representing (C2C), and study site will be treated as exogenous; all other variables in the paths will be treated as endogenous. Other variables that are identified as strongly associated with condition at baseline may be included as exogenous. Model fit indices will be evaluated (e.g., RMSEA, SRMSR, CFI).[149]

We will explore baseline levels of alcohol (probable AUD or not; AUDIT-C score $\geq$ 8),[122] PTSD (probable PTSD or not; PCL-5 score $\geq$ 31),[119] and depression (moderate depression or not; PHQ-9 score $\geq$ 10)[79] symptom severity as moderators of group-outcomes (linkage, utilization, mental health symptoms) associations. We expect that all groups that receive (C2C) will benefit from it, but these analyses will provide data on whether (C2C) is especially helpful for Veterans with more or less severe baseline hazardous drinking, PTSD and/or depression symptoms.

Aim 2 analysis plan (debriefing interviews). Data collected from debriefing interviews will be analyzed using template analysis.[139,140] The qualitative team will read all interview transcripts to identify participants' experiences participating in the (C2C) condition. Prototype templates will be created in electronic documents containing broad conceptual domains (e.g., what was your experience with (C2C), what was helpful/not helpful, what did you like/dislike about (C2C); (*Appendix G*) of experiences related to participating in (C2C). Analytic team members will combine prototype templates into a summary template (after reaching consensus on conceptual domains; we will aim for 100% agreement) with content grouped into categories within each conceptual domain. The process of categorization will allow for the identification of experiences described by participants. To establish analytic validity, the qualitative team will illustrate template content with verbatim quotations from participants. The quotations will provide verification of the accuracy of content labelling and grouping.[141]

### 5.7 Withdrawal of Subjects

We do not anticipate withdrawing participants without their consent for this aim. However, should a participant voluntarily withdraw from the study, we will seek their permission to use their data in the analysis. Should they not agree, we will remove their data from the analysis and store their data with study records. We do not plan to follow-up with participants who are withdrawn by study staff or voluntarily withdraw from the study. Per VA, participation in research is voluntary and study participants will not lose any benefits to which they are entitled and will continue to receive care. Should a Veteran be withdrawn from the study, we will be clear in communicating with the Veteran that they are still eligible for VA care.

## 6.0 Reporting

Drs. Cucciare and Humphreys will oversee the regulatory maintenance and reporting requirements. Study staff have received both VA and GCP training in regulatory maintenance and reporting requirements. Should an adverse event occur, study staff will complete the required reporting forms that will include the participant's study number and all relevant information about the adverse event. All staff will be required to immediately notify Drs. Cucciare and Humphreys about the occurrence of a serious or significant adverse event. Upon notification of the adverse event, Dr. Cucciare will respond promptly with the appropriate action. Should Dr. Cucciare be unavailable, Dr. Humphreys will be responsible for responding to a serious adverse event and will notify Dr. Cucciare as soon as possible. Serious adverse events will be reported within 24 hours of the occurrence as required to both the local and VA CIRB. An annual report will be submitted to the local IRB and project officer summarizing all adverse events. These procedures for reporting adverse events will apply to adverse events that occur during conversations about the study, the consent process, and semi-structured interviews. This study will be monitored by a Data Safety Monitoring Board.

## 7.0 Privacy and Confidentiality

All study data to include quantitative and qualitative interviews will be de-identified and stored in locked cabinets under triple locks (cabinet, office, front door) at each site respectively. Study staff collecting and storing PHI will have received training in steps to maintain participants' data security (e.g., using secure methods for storage such data). All electronic data to include PHI (e.g., birthdates) will be stored on an encrypted, password protected server behind the VA firewall. PHI will be coded and maintained in data crosswalk files that will also be stored on an encrypted, password protected server at both sites respectively. Data generated by the CDW (potentially eligible Veterans, data on care use) will be kept in an encrypted electronic folder on the Little Rock HSR&D COIN server (which is also encrypted). We will use randomly generated numbers to identify Veteran participants using an electronic "crosswalk" file that will be hosted on the Little Rock HSR&D COIN server. Debriefing interviews will be audio recorded using a VA approved audio recording device. All physical audio recordings (recorded using a VA-encrypted recording device – Philips Digital Recorder DPM-8000) will be kept in a secured (double locked) file cabinet. Once transferred to the HSR&D encrypted server (password protected), they will be deleted from the physical device.

This study will collect PHI including patient names, addresses, and telephone numbers (to contact participants to participate in the focus groups) and social security numbers so that we can reimburse participants for their study participation. In accordance with 38 USC 7332, this type of -1 Generated on IRBNet information will be kept confidential

and will not be disclosed in presentations, publications, or any other dissemination of the study results, or to anyone outside of the IRB-approved study team. In regard to SMS texting, project staff will only use text messaging after initial contact has been made with the veteran. Text messages will only be sent by VA research staff from VA issued cell phones. Text messages will not include any Veteran confidential information and will be limited to appointment and assessment scheduling and reminders. Research Investigator files will be destroyed six years after the end of the fiscal year when the research project has been completed per Records Schedule DAA-0015-2015-004. The VA CIRB, ISSO/PO and ACOS/RD will be notified immediately if there is inadvertent loss or disclosure of research data.

## 8.0 Communication Plan

This study has one site that is not engaged in research. Dr. Ed Post is a co- investigator located in Ann Arbor, Michigan. We will work closely with Dr. Post to ensure that his VA Medical Center Director and RD/IRB committees are aware that research is being conducted but the facility is not engaged. Dr. Post will not have access to identifiable data.
The protocol and all related documents shall be approved by the IRB and R&D Committee prior to enrollment of any subjects. The informed consent process shall be conducted only by appropriately qualified study personnel. The research team will regularly meet to discuss the study's progress and address any adverse events or unanticipated issues. The study coordinators will ensure all applicable IRB and RDC approvals are in place and will be in continuous communication with the principal investigators, Drs. Michael Cucciare and Keith Humphreys.

Drs. Cucciare and Humphreys currently meet weekly. During these meetings, we will discuss any changes to the protocol and informed consent. We will also discuss any Serious Adverse Events, Unanticipated Problems, or interim results that may impact conduct of the study. In our weekly study team meetings, we will discuss procedures and other study activities to ensure the study is conducted according to the IRB-approved protocol.
Once data collection is complete, Drs. Cucciare and Humphreys (both PIs) will work with their local IRB/R&D committees to ensure that their facility directors are aware that their sites are no longer engaged in research.

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