Original Protocol Title: Preventing Risky Drinking in Veterans Treated With Prescription Opioids

Renamed: Assisting Veteran in the Safe Use of Prescription Opioids

NCT02709317

Document date 03/08/2019

A. **Protocol Title**

1. **Full Protocol Title:** Assisting Veterans in the Safe Use of Prescription Opioids

2. **Date of Protocol Summary and Version #:** Date 03/08/2019; Version # 12

B. **Principal Investigator's Full Name and Degree:** James McKay, PhD

C. **Co-Investigator's Full Name and Degree**: David Oslin, MD

D. **Financial Sponsor** (Provide the name of the agency, organization, company or person providing funds for the research study.) **Department of Defense (DoD) (U.S. Army Medical Research and Materiel Command)**

E. **Grant** (Provide the name of individual who holds the grant and the grant number, if applicable.) **James McKay, 1 R01 DA037018-01**

F. **Protocol Number** (Provide the financial sponsor's protocol number, if applicable.)

G. **Institution(s) responsible for the project:**

1. For single-site studies - CMCVAMC is the only institution involved. Yes ☐ No ☒
2. For multi-center studies.
   - 2.1. CMCVAMC is the Coordinating Center in which the PI is the lead investigator. Yes ☒ No ☐ N/A ☐
   - 2.2. Provide the name of the Coordinating Center. Yes ☒ No ☐ N/A ☐ CMCVAMC
   - 2.3. List the name of the other sites involved. **VA Pittsburgh; University of Pennsylvania**
   - 2.4. Provide the FWA numbers for each of the other sites involved. 00001282 (VA Pittsburgh); 00004028 (Penn)

THE FOLLOWING INFORMATION MUST BE CMCVAMC-SPECIFIC, THAT IS, SPECIFIC TO WHAT WILL BE DONE WITH CMCVAMC-RECRUITED VETERANS.

H. **Background and Significance:** (Describe succinctly and clearly the past findings which justify the plan for this project. A summary of the relevant literature in the area of interest and reports of previous studies should be included.)

1. **Opioid Use in the Treatment of Pain**

   The prevalence of chronic pain continues to increase in the United States causing individual suffering and contributing to morbidity, mortality and disability. It has been estimated that over 100 million Americans suffer from chronic pain. In the Veteran population, improvements in battlefield medicine have resulted in large numbers of Veterans of Iraq and Afghanistan surviving injuries that in previous wars would have resulted in fatalities. A substantial percentage of these Veterans experience clinically significant pain and many require treatment with opioid analgesics. Clark et al. randomly selected and reviewed 300 charts of U.S. Veterans from a general medical population. They found that 50% of patients suffered from chronic pain and approximately 75% of the patients with chronic pain were prescribed at least one analgesic. Although non-steroidal anti-inflammatory drugs were the most commonly prescribed class of analgesics, 44% of patients receiving an analgesic received opioids. Wu et al. have also reported a rise in the prevalence of opioid use in young Veterans. Within the VA, chronic pain management and thus opioid prescriptions are almost exclusively provided within the primary care program.

2. **Risky Alcohol Use in Returning Service Personnel and Veterans**

   Alcohol misuse is the fourth leading cause of disability worldwide and is associated with increased mortality. Alcohol is, after nicotine, the most frequently abused substance among Veterans. The Veterans Health Study found that 12.1% of outpatients

had alcohol-related problems, and more recent studies found that 11-14% of Veterans in primary care screened positive for hazardous alcohol use. Several studies among Veterans recently returning from Iraq have found prevalence of alcohol misuse ranging from 24-39%, likely reflective of the younger age cohort. One other study found that of the OEF/OIF Veterans treated at VA hospitals in 2005, almost half screened positive on the AUDIT-C for likely risky/hazardous alcohol use. Alcohol misuse has tremendous individual and societal costs. For instance, Veterans who reported drinking during the previous year and who had a positive alcohol screening test experienced a 1.6 fold higher mortality rate over the subsequent 5 years than did patients who screened negative.

3. **Effects of Risky Alcohol and Drug Use in Veterans Being Treated with Prescription Opioids**

Although opioids can be a safe and effective therapeutic agent for many patients suffering from chronic pain, they have many known adverse effects including gastrointestinal complaints, cardiac problems, hormonal changes, immunologic effects, sleep disorders, sedation, addiction, and overdose. Of particular concern, there has been a substantial increase in fatal poisonings involving opioid analgesics. For example, the number of opioid-related fatal poisonings tripled from 4,000 to 13,800 deaths from 1999 through 2006 and approximately 40% of all deaths by poisoning in 2006 involved opioids. Opioid use is also associated with frequent use of emergency departments.

Many of these opioid-related overdoses or adverse effects involved the use of other substances including alcohol and benzodiazepines. Central nervous system depressant drugs such as alcohol and benzodiazepines, when combined with opioids, have an additive or interactive pharmacological effect on respiratory depression that may lead to serious adverse effects including death. Data from the *Drug Abuse Warning Network in 2010 revealed that pain relievers were involved in 23% of* emergency department visits involving the ingestion of both that alcohol and prescription medicine. Based on epidemiological data, alcohol is implicated more frequently in opioid-related deaths than any other substance. However, in 2006 approximately 50% of all opioid-related deaths in the US involved more than one substance, and benzodiazepines were found in 17% of these deaths. Also, benzodiazepines are frequent co-intoxicants in methadone-related deaths. These data highlight the importance of prevention of such adverse outcomes, which can be accomplished by screening patients receiving prescription opioids for risky/hazardous alcohol use, and providing interventions to those individuals who screen positive.

Similar issues have been noted with regard to other substance use in patients receiving opioids to treat chronic pain. In a recent national study of Veterans receiving opioid treatment for non-cancer pain, the strongest predictor of the development opioid abuse/dependence was a non-opioid substance use disorder. However, research results have raised some concern about how well Veterans receiving opioid medications are being monitored for other substance use problems. For example, Wu et al. found that nearly 80% of opioid prescriptions to young Veterans were given by primary care providers rather than pain specialists, and that only 31% of patients on chronic opioids had undergone urine drug testing to detect other drug use.

4. **Screening and Brief Interventions in the VA: Current Practice**

In 2004, the VA Office of Quality and Performance (OQP) began requiring annual alcohol screening using the AUDIT-C. Since implementation of this policy, medical record reviews conducted for the VA External Peer Review Program (EPRP) have shown that an average of 86% of patients are screened with the AUDIT-C. The vast majority of this screening occurs within primary care. In 2007, the VA implemented a performance

measure to incentivize the conduct of brief interventions and referral after a positive screen. This performance measure was temporarily associated with an increase in the delivery of brief interventions from a baseline of 5.5 % of Veterans who were screen positive getting a brief intervention to 29% after the implementation of the performance measure. These low rates of brief intervention and referral contrast sharply with patients' expressed desire for help. In the VA Large Health Survey, only 12% of heavy drinkers and 17% of very heavy drinkers reported getting the help they needed (30). Similarly, the seven-site ACQUIP study showed that only 30% of VA patients with alcohol misuse reported receiving advice to decrease or stop drinking, despite the fact that 83% reported contemplating or taking steps to change their drinking. Most recently concerns have been raised about the validity of screening done in clinical practice. As many as 61 percent of risky/heavy drinkers are not being identified by their clinicians, most likely because of improper screening techniques. Moreover, there was substantial variation between VA facilities suggesting marked implementation problems with screening. These data demonstrate that many patients with risky alcohol use are not receiving adequate diagnostic evaluations or preventive care to reduce their drinking. These problems take on increased significance with VA patients receiving opioid prescriptions, because of the potential for harmful interactions between opioids and alcohol, which can be compounded by the co-ingestion of other drugs.

To address some of these concerns, the VA is an industry leader in integrating a comprehensive set of services for mental health conditions in primary care. At the CMCVAMC, this program is known as the "Behavioral Health Lab" or BHL. During the last 5 years, there has been a complete reshaping of the VA's primary care system so that today it is organized as Patient Aligned Care Teams (PACT) similar to medical home programs, a key characteristic of which is the integration of mental health services with primary care. A driving force leading to the PACT model was the accumulation of evidence demonstrating that treating depression and alcohol misuse in the primary care setting within the VA leads to improved symptom-based outcomes, including reduced all-cause mortality. VA wide, BHL programs have served Veterans in two million patient encounters in less than five years and are a central aspect of the interdisciplinary care in the PACT programs.

The principles of the BHL program are to deliver patient-centered care while adhering to recommended treatment algorithms, modeled from the VA/DOD Depression Treatment Guidelines, including the use of structured assessments to facilitate care (instruments like the PHQ-9) at nearly every encounter. At the CMCVAMC and nationally, the BHL program is guided by a set of training guides entitled, "Foundations for Integrated Care." The training program was recently released to the field and embodies the evidence base for care management and co-located collaborative care. The goal of the program is to deliver care where the Veteran wants care and consistent with the resources needed to provide that care. <u>The BHL program is designed to be the principal point of entry for any Veteran seeking mental health care or who has screened positively on any mental health screening questionnaire including the AUDIT-C</u>. Thus, in general, the BHL program provides care to Veterans with milder disorders or those who need prevention services, while specialty care services are reserved for more complex or severe illness. Specifically for alcohol misuse, the BHL program provides a structured brief intervention (it is VA policy for Veterans to be administered the AUDIT-C and for anyone scoring a 5 or higher to be referred to BHL for clinical assessment). In reference to this proposal, the BHL program receives requests from the primary care team to conduct assessments and deliver brief interventions for Veterans who screen positive on the AUDIT-C. Currently more than 300 Veterans are evaluated in the BHL per month with 25% screening positive for alcohol misuse. This program will serve as the standard care arm of the study. Despite advances in screening, we are well aware that not all Veterans who screen positive on the AUDIT-C are referred for follow-up care

in the VA. Indeed, Maust et al showed that Veterans with a positive AUDIT-C score were 10 times less likely to be referred than Veterans who screen positive for depression or PTSD.

<u>February 2017 Amendment</u>
We amended the protocol to include subjects with a lower AUDIT score that would most likely NOT be referred by their Primary Care Provider (PCP) to the BHL for a Brief Intervention. However, as the National Institute on Alcohol abuse and Alcoholism (NIAAA) defines drinking while taking contraindicated medications as risky alcohol use: (https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking), and thus a BI is still warranted. For subjects enrolled in the study with a low AUDIT score, the study counselors will perform the BI.

<u>March 2018 Amendment</u>
We amended the protocol to eliminate the AUDIT score as part of our screening procedure. BHL will refer individuals who are drinking and on opioids, but no longer on AUDIT C results.

5. **Research on Brief Interventions for Risky Alcohol Use**
Two recent reviews have indicated that brief interventions delivered in primary care are effective in reducing rates of risky/hazardous alcohol use. However, two other reviews have indicated that brief interventions in primary care and other settings may not be effective for individuals with more severe alcohol problems. A recent study in a sample of Veterans showed that providing patients who had screened positive for risky alcohol use with a web-based brief alcohol intervention in addition to brief alcohol counseling from a primary care provider did not improve drinking outcomes over the primary care provider only control condition. However, several other studies have shown positive effects for web-based brief alcohol interventions in military samples.

6. **Beyond the Brief Intervention**
Although research on brief interventions (BIs) for risky alcohol use has generally shown positive results, several important gaps in evidence remain. First, there is considerably less information on whether such interventions are effective with other substances. Second, despite their efficacy, significant percentages of patients fail to respond to BIs. There is essentially no research on what types of interventions might be efficacious and feasible with individuals who continue to drink at risky levels after receiving a BI. Third, no studies have focused on the efficacy of BIs for risky alcohol use in patients receiving prescription opioids for pain.

One possible approach for BI non-responders is to provide additional BI sessions. Only a small number of studies have compared a single session of BI to an extended version of the same or similar intervention in primary care patients. Longabaugh et al. and Maisto et al. examined the impact of 1 and 2 additional sessions, respectively. Richmond et al. and Israel et al. tested the effect of 4 and 6 addition sessions, respectively, whereas Aalto et al. compared 2 and 6 additional sessions to a single session. The additional sessions in these studies were provided over periods ranging from a few days after the initial session up to 24 months later. Results varied across these studies, with some showing positive effects for the extended intervention and others showing no positive effects. <u>However, none of these studies tested an adaptive approach to BIs, in which follow up after the BI is determined by the patient's response, such as through the use of an algorithm directing additional sessions to individuals who did not respond to an initial session</u>.

In adaptive prevention and treatment interventions, the services provided to any given individual are tailored over time on the basis of response. In a typical adaptive

protocol, after an initial intervention, non-responders receive an augmented intervention or are switched to a new intervention. The tailoring variable is usually a measure of the targeted symptom or behavior (e.g., risky drinking, depression, tumor markers), assessed regularly over some period of time. Adaptive interventions have several important advantages over conventional interventions. First, they provide guidelines for how to modify interventions for non-responders, to improve outcomes for this group. Second, they lower patient burden and overall cost by reducing unnecessary additional interventions for patients who respond to the initial intervention.

7. **Preventing Risky Drinking and Other Drug Use in Veterans on Prescription Opioids**
We have developed an adaptive intervention designed to reduce levels of risky drinking and other drug use, in Veterans receiving prescription opioids for chronic pain. This patient-centered intervention provides integrated screening, brief intervention, monitoring, and extended prevention services that are delivered through a combination telephone calls, and text messages. Moreover this intervention is ideally suited to be disseminated within the primary care/mental health initiatives for patient centered medical home teams. The intervention is intended for Veterans who are receiving prescriptions for daily doses of opioids for pain and/or opioid replacement therapy; who also screen positive for risky/hazardous drinking. At the beginning of the intervention, a brief intervention (BI) is provided to reduce alcohol to safe levels, and a health screening is provided to flag other medication use that could interact negatively with opioid use (e.g., benzodiazepines). Following administration of the BI, alcohol use is monitored for one month to determine whether the intervention has been effective. Veterans who reduce their drinking to non-hazardous levels will continue in a monitoring track, which consists of tailored text messages and brief monthly telephone contacts. Veterans who continue to use alcohol at unsafe levels will instead be placed in a track that provides tailored text messages and more frequent telephone calls. In addition to monitoring, these calls provide further prevention to help the Veteran reduce alcohol use to non-hazardous levels. These services address motivational issues and identify more effective ways to cope with stress and other factors that trigger unsafe substance use.

8. **Rationale for Intervention Components**
   a. **Extended monitoring in responders. BIs typically do not provide follow-up contacts, which raise questions about the need for ongoing monitoring in responders. However, studies have indicated that Veterans receiving prescription opioids are at heightened risk for a number of adverse health outcomes, and would be at even higher risk if they were to resume hazardous drinking. Brief monthly monitoring calls, supplemented by text messages, represent a low-burden, low-cost method to detect the resumption of hazardous alcohol use. Providing monitoring over 12 months allows for the possibility that some Veterans will do well initially, but increase their use of alcohol at a later point, perhaps due to stressors related to the transition to civilian life, including family or employment problems. If increased substance use occurs, additional prevention interventions can be delivered.**
   b. **Enhanced prevention efforts for non-responders. Examination of results from BI studies suggests that 20-50% of participants who receive these interventions do not reduce alcohol use to non-hazardous levels, with a higher percentage of non-responders among individuals who are also using drugs. Very few of these individuals are appropriate for specialty addiction treatments which typically have an abstinence orientation and are designed for people with more severe substance use problems. Therefore, additional prevention services are needed that are feasible to implement, of relatively low burden, and acceptable to Veterans. The combination of text messages and brief prevention counseling provided via the telephone meets these requirements. In our prior work (see below), we have**

demonstrated that it is possible to deliver interventions to increase motivation and coping abilities via relatively brief telephone calls, with good fidelity to treatment manuals. These interventions directly address the factors that contribute to nonresponse to brief interventions—low motivation for change, low self-efficacy, and problems with coping with stressors that precipitate drinking episodes.

c. Inclusion of text messaging (SMS) interventions. Mobile interventions, specifically SMS interventions, are well suited for ongoing monitoring and prevention interventions for risky alcohol and drug use because they can be tailored to the individual through decision support features, are flexible enough to meet individuals in their natural environment, and can adapt to their current needs in real-time using ecological momentary assessment. Numerous studies have shown that text messaging can improve outcomes across physical and mental health disorders. SMS interventions have been found to have small-to-moderate effects against no treatment controls with the largest effects being for smoking cessation and HIV medication adherence. In the largest SMS study to date, "txt2stop," an SMS intervention for smoking cessation doubled quit rates in a sample of over 5,000 individuals in the UK.

Recent reviews suggest that the addition of text messaging and other prompts improves the effects of web-based interventions, highlighting the use of SMS as a component to enhance other interventions. Although messaging interventions may work via mechanisms similar to those of telephone-based interventions (e.g. by catching individuals in their natural environment, reaching people in the moment without a computer connection), they offer several unique benefits that can enhance phone-based interventions. Text messaging allows for increased confidentiality, invulnerability to missed calls, and convenient continual viewing of messages sent and received. Text messages are less intrusive than phone calls, expend less labor, and do not require the phone to be active (the message will be resent for several days until the phone is active. This is especially important as low income individuals may have their phones turned on and off due to difficulties in paying bills.

SMS interventions have several other important features that warrant their integration into prevention models. First, messaging interventions inherit the benefits of computer-based interventions (e.g. low cost, standardized, individualized, adaptable and tailored, allowing for data collection) but there is no need for an internet connection or a computer. Second, unlike mobile applications (apps), SMS interventions do not require a smart phone, custom software programming for specific phones, or application updates, and are accessible on most phones, making the intervention significantly more accessible and generalizable than smart phone apps. Third, SMS-ready phones can perform nearly all of the functions of stand-alone ecological momentary assessment (EMA) devices without additional hardware or custom programming. There is an emerging literature on the using of text messaging to capture EMA data and results reveal outcomes similar to those of personal digital assistants (PDAs) and interactive voice response technology (IVR). Additionally, most studies have also indicated that SMS interventions are well accepted by participants as an intervention or adjunctive intervention and messaging is seen as more personal than that of other automated approaches. Muench, Adams, McKay and Morgenstern found that only 2 of the 125 individuals screened for a study of treatment for substance abuse did not have a mobile phone and all participants' phones were SMS ready with 60% of participants having unlimited messaging plans. Interestingly, weekly SMS questions about appointment attendance were perceived to be as helpful to keep appointments as daily reminders highlighting the fact that minimal prompts may be all that is needed to reinforce change.

In our previous work, we found that only 2 of the 125 individuals screened for a study of treatment for substance abuse did not have a mobile phone and all participants' phones were SMS ready with 60% of participants having unlimited messaging plans

9. **Prior Studies. We have conducted a series of studies that examined the efficacy of the telephone for the provision of follow-up care to individuals with risky drinking or substance use disorders. The interventions that were evaluated in these studies were telephone care management for heavy drinkers in primary care, motivational interviewing for patients with alcohol or cocaine use disorders who failed to engage in or dropped out of treatment, and telephone continuing care for patients with alcohol or cocaine use disorders who had completed several weeks of addiction specialty care treatment.**
    a. **Telephone Care Management for Heavy Drinkers in Primary Care. Helstrom and colleagues randomized Veterans who screened positive for risky/hazardous alcohol use in primary care to a standard session of brief advice from their primary care provider or to the brief advice plus 3 telephone care management (TCM) follow-up sessions at 3, 6, and 9 months. At the 12-month follow-up, rates of risky/hazardous drinking were 51% in the TCM condition vs. 56% in the usual care condition (*p*= ns). The results of this study highlight the persistence of risky drinking in Veterans (i.e., almost 50% were still engaging in risky drinking after 12 months), and suggest that providing three follow-up prevention sessions is probably not adequate to decrease the rate of risky drinking in this population.**
    b. **Motivational Interviewing (MI) Delivered by Telephone. We recently completed two studies in which patients with alcohol or cocaine use disorders who dropped out of treatment were provided with 1-2 telephone-based MI sessions in an effort to re-engage them. Half of the participants in these two studies were Veterans. The MI sessions were audio recorded, and coded to assess the quality of the MI. On average, MI fidelity as measured by the MITI met or exceeded "beginning proficiency" thresholds. The skill level for MI-consistent strategies was at threshold level and the use of "fundamental" MI strategies and skill level was above threshold level. Results indicated that MI designed to re-engage patients in their original treatment program produced better alcohol use outcomes than MI coupled with a menu of other treatment options.**
    c. **Telephone-Based Alcohol Disease Management Study. We developed an 18-month telephone-based intervention, which we compared to standard care in 252 alcohol dependent patients who completed 3-4 weeks of outpatient treatment. Telephone Monitoring and Counseling (TMC) consisted of 20-minute telephone calls that were provided weekly for 8 weeks, twice monthly for 10 months, and monthly for the final 6 months. Each call began with a 5-minute structured assessment of risks and protective factors, followed by Cognitive-Behavioral Therapy (CBT) techniques focused on developing coping responses to the most pressing problem identified in the assessment. During the 18-month treatment period, rates of any alcohol use (OR= 1.88) and any heavy alcohol use (OR=1.74) were significantly higher in standard care (TAU) than in TMC. Significant group x time interactions were obtained on the percentage days alcohol and heavy alcohol use, in which the advantage for TMC over TAU increased over time. Subgroup analyses over the full 24 month follow-up period showed effects favoring TMC over TAU on percent days drinking were greater in women (OR=0.47, p=.04) and those with prior treatments (OR= 0.59, p= .02); and in those with social networks that supported continued drinking (OR=0.44, p=.02) and low readiness to change (OR=0.53, p=.05) after 3 weeks of IOP.**
    d. **Telephone-Based Cocaine Disease Management Study. In a similar continuing care study with cocaine dependent patients (N=321), there were interactions between**

cocaine and alcohol use at baseline and the continuing care conditions (p= .03) on the primary outcome, a measure of abstinence from cocaine, other drugs, and heavy alcohol use (confirmed by urine toxicology tests). In patients with any days of cocaine or alcohol use in the 30 days prior to baseline (i.e., the week prior to intake and the first 3 weeks of treatment), abstinence rates were higher in TMC than in TAU, with the treatment effect larger in those who had been drinking at baseline (OR=2.47, p= .007) than in those who had been using cocaine (OR=1.95, p= .04). Conversely, in patients with no days of cocaine or alcohol use in the 30 days prior to baseline, there were no treatment effects. Of note, incentivizing participation in the telephone sessions dramatically increased the number of sessions completed, but did not further improve outcomes.

e. Summary of Findings from Our Research Program. These studies demonstrate our ability to recruit large samples in a timely fashion, enroll Veterans who are engaging in risky drinking into research studies, deliver interventions over the telephone, and maintain high follow-up rates across periods as long as 24 months. Three of these studies also provide evidence to support the effectiveness of enhanced or extended interventions for patients who do not evidence a good initial response to alcohol/drug treatment.

I. **Purpose of the Project:** (Clearly provide the purpose of this research project.) **In this application, we propose to test an integrated prevention intervention, designed to reduce rates of risky drinking in Veterans receiving prescription opioids for chronic pain management or opioid replacement therapy. For Veterans on opioid replacement therapy, they must have a chronic pain diagnosis. This adaptive, patient-centered intervention provides integrated clinical assessment, brief intervention, monitoring, and extended prevention services delivered through a combination of telephone calls, and text messages.**

J. **Describe the Research Questions or Hypotheses** (that is, what questions are you trying to address by conducting the research.**)**

1. **Primary objective: To compare the effectiveness of a 12-month prevention intervention (PI) with a brief intervention only group (BIO) over an 18-month follow-up period, for Veterans treated with prescription opioids and who are engaging in risky/hazardous drinking, based on NIAAA guidelines.**
   - ***Hypothesis 1*: PI will produce better outcomes than BIO, as indicated by lower rates of risky/hazardous alcohol use across the follow-up period.**
2. **Secondary objectives: To examine secondary outcome measures, moderator effects, and mediation effects:**
   - ***Hypothesis 1*: PI will produce better outcomes than BIO on frequency of heavy drinking, biological measures of heavy drinking (i.e., GGT and CDT), urine toxicology tests to assess other drug use, depression, and pain.**
   - ***Hypothesis 2:* Rates of opioid overdoses will be lower in PI than in BIO**
   - ***Hypothesis 3*: Intervention effects will be greater in higher-risk Veterans, including those with higher prescription opioid dosages, co-occurring benzodiazepine use, poor social support, and low readiness for change.**
   - ***Hypothesis 4*: Results favoring PI over BIO on risky drinking will be mediated by greater readiness for change, self-efficacy, and coping.**

K. **Primary Outcome Variable(s):** (Define the primary outcome variable(s) used to support the study objectives (e.g. if the objective is to show that treatment A is superior to treatment B in the treatment of subjects with essential hypertension, the primary outcome variable is blood pressure measurement.) **The <u>primary</u> outcome measure will be rates of <u>risky drinking</u> (i.e., more than 4 drinks at any one sitting or more than 14 drinks/week for men; more than 2 drinks at any one sitting or more than 7 drinks/week for women) (5) within each follow-up period, as determined by the TLFB.**

L. **Secondary Outcome Variable(s):** (Define the secondary outcome variables. Such measured variables should also include the timing of measurement.) **Secondary outcomes in the study will be self-reported frequency of heavy drinking days (TLFB), biological measures of alcohol use (%dCDT and GGT), urine toxicology tests to assess other drug use, VA records of opioid overdoses, depression, and pain.**

M. **Study Design and Methods:**

1. Is this a clinical trial? ☒YES ☐NO
   - 1.1. If yes, what type? Check all that apply.
     ☐ **Phase I** ☒ **Phase II** ☐ **Phase III** ☐ **Phase IV**
   - 1.2. If yes, this study must be registered on Clinicaltrials.gov.

2. **Design**
   - 2.1. What research methods will be used in the project? Check all that apply.

☒ Surveys/Questionnaires	☒ Interviews	☒ Audio Taping
☐ Behavioral Observations	☐ Chart Reviews	☐ Video Taping
☐ Focus Groups	☒ Randomization	☐ Double-Blind
☒ Control Group	☐ Placebo	☐ Withhold/Delay Treatment
☒ Specimen Collection	☐ Deception	☐ Telephone Survey
☐ Other (Describe)		

   - 2.2. Describe how randomization or other treatment assignment will be made. **Veterans who meet criteria for participation will be randomly assigned to one of the two treatment conditions. Urn randomization will be used to balance the groups on three factors: gender, benzodiazepine or other drug use, and age. We will also be blocking on whether the person admits use or not when we do the randomization, so we get equal numbers of non-users in each condition. Urn randomization is a kind of biased-coin randomization where probability of being assigned to a group decreases if the group is overrepresented and increases if the group is underrepresented. As the sample size increases, the randomization shifts from perfect balance to complete randomization.**
   - 2.3. For retrospective research studies, provide the "look-back" period. (e.g., December 1, 1999 through December 31, 2008.) **n/a**

3. **Study Duration**
   - 3.1. Provide the estimated length of time to enroll all subjects and complete the study. **2.5 years of enrollment, but 5 years total for study start up, enrollment, completion, and analyses.**
   - 3.2. Explain the expected duration of subject participation including any follow-up.**18 months for patients enrolled prior to 4/1/2019; 12 months for patients enrolled after 4/1/2019**
   - 3.3. Specify the projected date of completion of the proposed study. **5 years from date of funding.**

4. **Drug Information** (If not applicable state, "Not Applicable.") **Not Applicable**
   - 4.1. Specify if the drug or biological agent is:
     - 4.1.1. FDA approved
     - 4.1.2. Used for off-label purposes
     - 4.1.3. Not yet FDA approved**.**
   - 4.2. Include the FDA Investigational New Drug (IND) number for all non-FDA approved and off-label drugs, biological agents or nutritional supplements. If not applicable state, "Not Applicable."
   - 4.3. Provide all relevant information about the drug
   - 4.4. Explain any wash-out periods, rescue medications permitted and any type of medications not permitted while enrolled in the study.
   - 4.5. Describe blinding and un-blinding procedures.

4.6. Include the dosage, route of administration, previous use, and the safety and efficacy information on any drug used for research purposes.
4.7. Describe rationale for the dosage in this study.
4.8. Justify why the risks are reasonable in relation to anticipated benefits and/or knowledge.

4.9. Describe where drug preparation will be done.
4.10. All drugs for CMCVAMC subjects must be dispensed through the VA investigational pharmacy.
4.11. Describe where the study treatment will be administered.
4.12. Describe plan for tracking a non-compliant treatment study subject.
4.13. Summarize any pre-clinical data.
4.14. Describe the process for the storage, security, dispensing and return of an investigational drug.

5. **Investigational Device** (If not applicable state, "Not Applicable.") **Not Applicable**
5.1. The Investigational Device Exemption (IDE) number must be submitted for all significant risk devices and if an IDE exists for a non-significant device.
5.2. Significant Risk or Non-significant Risk - If a device is not approved by the FDA, specify whether or not the sponsor has determined this device to be a "significant risk" or "non-significant risk" as defined by the FDA.
5.3. Provide all relevant information about the device.
5.4. Describe blinding and un-blinding procedures.
5.5. Specify if device is:
5.5.1. FDA approved
5.5.2. Used for off-label purposes
5.5.3. Not yet FDA approved.
5.6. Explain if the investigational device will be delivered and/or stored by the Principal Investigator or Pharmacy Services.
5.7. Describe the process for the storage, security, dispensing and return of an investigational device.
5.8. For research involving an investigational device, describe the SOP or plan for device control.
5.9. Address how the device will be stored in such a way that only research staff associated with the protocol will have access to the device.
5.10. Describe measures that will be put into place to ensure that the device will only be used in participants of this research protocol.

N. **Does this project involve international research?** ☐YES ☒NO
1. *For further instructions refer to VHA Directive 2005-050, Requirements for Conducting VA-Approved International Research Involving Human Subjects, Human Biological Specimens, or Human Data*
2. *VHA Handbook 1200.05 definition of international research - VA international research is any VA-approved research conducted at international sites (not within the United States (U.S.), its territories, or Commonwealths); any VA-approved research using either human biological specimens (identified, de-identified, or coded) or human data (identified, de-identified, or coded) originating from international sites; or any VA-approved research sending such specimens or data out of the U.S. (see par. 56).* ***NOTE:*** *For the purposes of this Handbook, research conducted at U.S. military bases, ships, or embassies is not considered international research.*

O. **Study Procedure**
1. **Study Procedures**
Outline all study procedures - (If necessary, include a table or flow chart, showing the schedule of the procedures and interactions. Distinguish between interventions that are experimental and carried out for research purposes vs. those that are considered

standard of care. Routine procedures that are performed solely for research purposes should also be identified.) **Recruitment for this study will happen in a few ways. For the majority of our potential participants, we will be using pharmacy records and reaching out by letter and phone call (Letter and phone script provided). We will use VA pharmacy records to identify Veterans who are currently being prescribed daily opioid medication for the treatment of chronic pain. Veterans already in treatment for alcohol use disorders (AUD) will then be excluded from the study. Veterans in treatment for opioid use disorders who are on a daily medication assisted regimen (i.e. OTP program) will be included as long as they have a chronic pain diagnosis and no AUD. For potentially eligible patients, we will send an encrypted email to the prescribing physicians (See email content below). If a PCP objects to our intent to recruit their patient, we will not send that Veteran a letter. If the clinician does not object to the study team contacting the potential subject we will contact potential subjects via letter to describe the research study and follow-up with a telephone call to invite them to participate (phone script provided). We respect the time of all the Veterans we are recruiting for this study. We want to ask these other questions because if we can clearly determine a Veteran is not eligible, we do not want to make them come in for a long consent/screening/baseline appointment and then be told they cannot participate. The Veteran may have to pay to take public transportation to the VAMC, or may be upset after completing the long first session and finding out they cannot participate. We want to limit unnecessary costs and agitation experienced by Veterans we are recruiting.**

There are a few potential outcomes of the screening call:

- **If they are not eligible for the study and the Participant will not be contacted again. No referral or communication of results will be made. If they are ineligible due to screening positive for a substance use disorder (by having 5 or more symptoms on the exclusion checklist), then they are drinking (or using) at too high a level and the results of this screening will be communicated to BHL for further clinical care.**
- **If they are not currently receiving mental health services at the MHC, and eligible: If Veteran decides to participate, a study counselor will complete the Brief Intervention only after participant has been consented to participate in the study and admits to any drinking. If the counselor determines their alcohol use is severe enough to necessitate more intensive treatment (i.e. inpatient treatment), the Veteran will be referred to the higher level of care and will be removed from our study. If Veteran decides not to participate, the technician will thank them for their time and end the call. A research note describing the outcome of screening call will be created in CPRS.**
- **If they are currently receiving mental health services at the MHC, and eligible: If Veteran decides to participate, a study counselor will complete the Brief Intervention only after participant has been consented to participate in the study. If Veteran decides not to participate or is later found to be ineligible, standard care through the MHC will continue as if he/she had never been contacted about the study. A research note describing the outcome of screening call will be created in CPRS.**
- **If they are not currently receiving mental health services at the MHC, and ineligible: A research note describing the outcome of screening call will be created in CPRS.**
- **If they are currently receiving mental health services at the MHC, and ineligible: Standard care will continue through the MHC as if the Veteran had never been referred to the study. A research note describing the outcome of screening call will be created in CPRS.**

- **It is possible through the course of receiving care at the CMCVAMC that a Veteran has received a BI in the past. However, this treatment could have occurred far enough in the past (i.e. greater than 3 months) that the BI would need to be repeated. As we cannot ensure a Veteran has received a recent (within the past 3 months) BI through the MHC, the study staff will perform the BI's for those Veterans.**
- **If enrolled in the Opiate Treatment Program and eligible: If Veteran decides to participate, a study counselor will complete the Brief Intervention only after participant has been consented to participate in the study. If Veteran decides not to participate or is later found to be ineligible, standard care through the OTP will continue as if he/she had never been contacted about the study. A research note describing the outcome of screening call will be created in CPRS.**
- **If enrolled in the Opiate Treatment Program and ineligible: Standard care will continue through the OTP as if the Veteran had never been referred to the study. A research note describing the outcome of screening call will be created in CPRS.**

Encrypted email to prescribing clinician:

Dear Dr. XX,

One of your patients, XXX, may be eligible to participate in a study titled "Assisting Veterans in the Safe Use of Prescription Opioids." Please see their information below.

Name: <<Last>>, <<First>>, <<Middle>>
Last 4: <<Last4>>

Our recruitment entails sending Mr./Ms. XX a letter and then following up with him/her via phone one week later.

If you have any questions or concerns please do not hesitate to contact the study's principal investigator, James R McKay at james.mckay@va.gov

Thank you,

Margaret Lawlace

Referrals from BHL
In addition, we will take referrals from BHL. BHL will refer subjects based on any alcohol and/or use of opioid. If a Veteran expresses interest in our study to a member of the BHL team, study staff will be notified and will call the Veteran to further explain the study and perform a screening (phone script provided).

In this scenario, there are a few potential outcomes of the screening call:
- **If referred from the BHL and eligible: Results of screening call and patients' decision to participate will be communicated to the BHL. A counselor from the study team will perform the Brief Intervention. If participant decides not to participate, services at the CMCVAMC will continue as if participant had never been referred to the study. A research note describing the outcome of screening call will be created in CPRS.**
- **If referred from the BHL and ineligible: Results of screening call and ineligibility to participate will be communicated to the BHL. Services at the CMCVAMC will continue as if participant had never been referred to the**

study. A research note describing the outcome of screening call will be created in CPRS.

We will ask potential participants if they have texting capability during the initial phone screen. Cost of using the phone for texting and receiving calls will be covered by the participant but minimized as much as possible. In previous work, we found that only 2 of the 125 individuals screened for a study of treatment for substance abuse did not have a mobile phone and all participants' phones were SMS ready with 60% of participants having unlimited messaging plans.

For those who are potentially eligible following the phone screen (and interested in participating), the next step is coming to the VA for consent. After consent, subjects will complete the first research visit. Final eligibility is determined after consent using the SCID and MINI. If after learning more about the study during the consenting process, the Veteran decides not to consent, or if they are ineligible following the SCID and MINI, then the Veteran will continue to receive services at the CMCVAMC to which they are eligible and entitled to. This could include services through the BHL or MHC. Similarly, Veterans can also elect to stop their participation in the study and can withdraw without penalty in writing using the revocation form at any time after they have consented to the study. In this case, their normal care at the CMCVAMC will continue.

Veterans who meet criteria for participation will be randomly assigned to either receive the usual care (that which they would have gotten if they had not chosen to be in the study); or Prevention Intervention (PI).

As a result of relaxing our inclusion criteria, it is likely that we will randomize Veterans who have not consumed alcohol in the past three months. For those Veterans, we will monitor their alcohol use during the research follow up visits at 3, 6, and 9 months. If they report having a drink of alcohol, we will then begin which treatment arm they had been randomized to. If the Veteran does not report taking a drink prior to the 9 month follow up, they will simply continue with the 12 and 18 month follow ups but will never have the Brief Intervention or Prevention Intervention.

<u>Brief Intervention (BI)</u>
Both groups will have received or will be scheduled to receive Brief Intervention (BI). A brief intervention includes providing feedback linking the Veteran's drinking to their health issues, in addition to providing education and advice about recommended drinking limits, and how to reduce alcohol use. In general, a BI involves increasing an individual's insight about the risk of drinking on opiates, and how to cut down. However, each Veteran presents with a different situation, and thus the BI can be flexible in terms of content. Sometimes the BHL will send the NIAAA workbook "rethinking drinking" to a Veteran, sometimes they won't. Sometimes a Veteran will get a follow up call, and sometimes they won't. It depends on what the Veteran needs. So in terms of what exactly the research staff will do during BI's, it will follow a similar structure to the BHL BI's (raise insight, identify strategies on how to reduce) but the details on how to accomplish those goals will vary based on each Veteran's individual situation.

For Veterans not enrolled in the Mental Health Clinic (MHC), study staff will administer the BI since as a result of broadening our inclusion criteria these are individuals that would likely not be serviced by BHL. If during the baseline visit study staff determine that the Veteran's drinking warrants a referral to the Behavioral Health Lab (BHL) then the BHL will administer the BI. For Veterans

enrolled in the MHC, the study team will administer the BI. Study staff have worked with the BHL nurses and have all of their material and can perform BI according to standards set in the BHL protocol. Study staff will get ongoing supervision from the BHL staff, to make sure that we are following their protocol. The research counselors are Masters level clinicians trained in recovery counseling and the administration of Brief Interventions. On average, BI's take about 20 minutes, and will be done over the phone. Subjects will not be compensated for the BI done for study purposes. While not all BI's require a follow up call, following the same procedures done by the BHL, the research staff providing the BI at times will complete one or two follow up calls one month after the initial BI, to check in on an individual's progress.

The reason why study staff needs to provide BI to subjects recruited from MHC is that BHL provides services to primary care patients. Patients already using mental health specialty care are not typically referred back to BHL for interventions like BI.

Brief Interventions for Pittsburgh Site
Research counselors at the Crescenz VAMC in Philadelphia will perform all BI's for Veterans recruited from the Pittsburgh site. These BI's will follow the same structure as BI's that occur at the Crescenz VA, they will be over the phone and take about 20 minutes to complete.

Brief Intervention Only Group (BIO)
This group only receives a Brief Intervention (BI) that is recommended in response to risky alcohol use. Participants in this group will have 6 study visits as described below.

Prevention Intervention Group
Participants in this group also will get a Brief Intervention. In addition, they will get text messages as described in the next section.

PI Overview. We have designed an adaptive monitoring intervention, delivered primarily through text messages and brief telephone calls that can provide extended prevention services for Veterans engaging in risky/hazardous alcohol use. These services address motivational issues and identify more effective ways to cope with stress and other factors that trigger unsafe alcohol use. The intervention is adaptive in two ways. Veterans who reduce alcohol use to safe levels will be placed in a monitoring track, which consists of tailored text messages (see appendix which contains examples of text messages to be used) and brief monthly telephone contacts. Conversely, Veterans who continue to use alcohol at hazardous levels will instead be placed in a track that provides tailored text messages and more frequent telephone calls. In addition to monitoring, these calls provide further prevention/brief intervention services to help the Veteran reduce alcohol use to non-hazardous levels and reduce the use of benzodiazepines and other potentially hazardous drugs. Phone calls will be audio recorded to ensure adherence of the Research prevention counselors to the manuals. We will remind subjects that calls are being recorded and they can refuse the recording, but still participate in the research call.

The Wellpass system will automatically send text messages to Veterans either within messaging windows or at specific days and/or times depending on the goal of the message (e.g. appointment reminder vs. motivational message vs. just-in-time support for at-risk Veterans). On average, Veterans will receive between 1-14 tailored text messages per week, depending on whether they are reducing

drinking to below risky levels. In addition to sending tailored messages as described above, the SMS system will conduct on average weekly ecological assessments. (Ecological assessments are research questionnaires that happen in the "real world." Ours will entail text messages such as: "Have you met the goal you set for yourself over the past week? Please respond 1 (not at all), 2 (somewhat) or 3 (mostly)." These are different from the motivational messages and are used to track progress and inform phone counseling sessions.) Veterans who are having trouble meeting their goals will receive more assessment messages. Veterans who initially reduce alcohol use to safe levels and are therefore placed in the monitoring track will transfer over to the more intensive prevention track if their alcohol use increases to risky levels at some point in the 12-month intervention. Veterans whose alcohol or drug use escalates to DSM-V moderate to severe substance use disorder levels will be given a referral to specialty care and their progress will be evaluated at regular follow-up visits.

Although the research counselors will be able to alter the messaging frequency and scripts based on the progress of the Veteran, decision support rules based on change will help guide messaging content and frequency to reduce research counselor burden. The system will alert research counselors to reductions in motivation or other red flags that may indicate the Veteran needs more support and will include proactive "help messages" for Veterans in the moment, which will trigger just-in-time messages and system alerts. In addition, Veterans can decide on the minimum and maximum number of messages they wish to receive per week. The text message conversations between our research counselors and the study participant will also be recorded and kept in an encrypted database.

All participants will be using their own cell phones during their participation in the study. We will instruct participants to inform us if they lose/damage their phone. However, we will not replace Veterans' personal cell phones. If data security is breached, we will follow VA and HIPAA mandatory disclosure procedures. If data is lost but not breached (e.g. to server malfunction), we will assess the situation and alert the study sponsor.

<u>Study visits</u>:
In addition to the intervention, all participants will be seen at 3, 6, 9, 12, and 18 months post baseline for research follow ups. Participants enrolled after 4/1/2019 will only be seen at 3, 6, 9, and 12 months post baseline for research follow ups. These will be done at the CMCVAMC and will take approximately 1.5 hours. The schedule of assessments (all of which are for research purposes only and not part of standard care) is as follows: SCID and MINI (B); Blood samples (%dCDT and GGT) (B and 18m); Time Line Follow-Back, SIP (B, 3, 6, 9, 12, 18); Drug urine toxicology tests (B, 3, 6, 9, 12, 18); Self-efficacy, Coping, Social Support, Readiness to Change, pain, depression, quality of life (B, 3, 6, 9, 12, 18).

<u>October 2015 Amendment</u>
Because of the potential subjects were concerned about the "integrated" aspect of the study and how it might influence their clinical care, we submitted an amendment to remove the integration of the study and leaving research notes summarizing their status will no longer be the default. We have contacted the DoD about this change, and they are fine with it. The "integrated" nature was not an important piece. At a yearly progress meeting for DoD grant recipients, most of the other SUD related project have made it a point to NOT integrate their interventions with veterans[1]s medical care, as it sharply reduces recruitment rates.

We have randomized 7 subjects. We will notify them of the change, and re-consent them.

<u>January 2016 Amendment</u> - An amendment to the protocol has been made adding two sites to the study, with the CMCVAMC being the coordinating site. We are adding VA Pittsburgh as well as recruiting veterans not seen by the CMCVAMC at the University of Pennsylvania site. These sites are being opened up to address the poor recruitment numbers at the CMCVAMC site.

There is also a change to where the data is housed. Now instead of data being housed on a secure server in the VA, it is housed on a secure server at the University of Pennsylvania. An Off-Site Storage form is included. Additionally, the Penn/PVAMC MOU is included.

Paper based data will ultimately be kept at the CMCVAMC. However, electronic data will be combined and stored at Penn. The direct data entry can be done at Pittsburgh, CMCVAMC, and Penn, as long as there is internet access.

<u>July 2016 Amendment</u> – An amendment to the protocol has been made to change the server back to the secure server at the VA. The reason for this is an issue with software and being able to get through the VA firewall for data entry.

Paper based data will ultimately be kept at the CMCVAMC. Electronic data for Pittsburgh and CMCVAMC will also be stored at the CMCVAMC. Penn data will be stored at Penn as there is no way to access the VA server from outside the VA.

<u>January 2017 Amendment</u> - Previously Veterans had to score a four or greater (females 3 or great) on the AUDC during the initial phone screen to be eligible to participate in the study. We have lowered this threshold to a score of two, as this score can still be indicative of regular/heavy alcohol use that would place Veterans prescribed chronic opiates at risk.

According the NIAAA, any alcohol use with contraindicated medications (like opiates) is considered risky:

Certain people should avoid alcohol completely, including those who:

- ***Plan to drive a vehicle or operate machinery***
- ***Take medications that interact with alcohol***
- ***Have a medical condition that alcohol can aggravate***
- ***Are pregnant or trying to become pregnant***

(https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking)

Risky drinking will be ascertained during the AUDIT-C. Usually when administering the AUDIT-C, individuals will give vague answers (i.e. "every now and then") that require follow up questions. For instance, if a Veteran affirms a period of time when they drank 6+ drinks in the past year, the interviewer could ask, "When was the last time that happened?" When asking about consumption the interviewer will be able to ascertain if the Veteran's level of consumption meets this threshold (questions two and three) either with the Veteran's initial response or with follow up questions.

We have also included language on how this will affect standard care through the BHL. As Veterans will be referred with lower levels of alcohol use (but still risky), after BHL triage it is possible that these Veterans will not receive a brief intervention.

Further, our business office is moving away from using petty cash to compensate research participants. Instead, we are switching to the Greenphire ClinCard system. ClinCard functions like a Visa debit card, and money can be loaded on to the card remotely by study staff. Our protocol has been updated to describe the system, how it functions, how Veterans will be paid.

<u>March 2018 Amendment</u>- We are changing the name of the study to something that sounds less threatening to Veterans who may fear losing their opiate prescription if they admit to drinking alcohol. We plan to change it to "Assisting Veterans in the Safe Use of Prescription Opioids."

Further, we plan to change the inclusion criteria to include Veterans on prescription opiates for chronic pain regardless of whether or not they admit to drinking alcohol.

As part of broadening the inclusion criteria we plan to add a third group to the adaptive intervention. We will enroll and randomize the Veterans who do not admit to drinking and place them in a monitoring category where we continue to assess them and if they admit to consuming any amount of alcohol we would then transfer them to the treatment arm into which they had been randomized. This change is a significant change to the study but does not change the aims or outcomes and it does not increase the risk. It is a change supported by the DOD as a way to increase enrollment and reach veterans that we think may be less truthful about their alcohol use out of fear that they will have their opiate prescriptions taken away.

Following up those who initially deny drinking will provide important data for the VA. The yearly AUDIT screening appears to be underestimating the numbers of vets who are drinking alcohol. If our data indicate that a significant percentage of those who deny drinking at the start of the study end up reporting drinking later in the follow-up, it will be in indication that at risk patients (i.e., those on opioid meds) are at risk due to underreporting of their drinking, which could be an unintended consequence of the current VA policies.

We also will no longer be using the AUDIT-C.

Additionally, we have decreased the total n for the study to 150 from all sites. That is, 200 subjects from all sites being randomized (with 150 participants drinking and entering TX phase and 50 participants not drinking (25 at CMCVAMC and 25 at Penn).

Moreover, there is a personnel change. Max Stern is no longer a Research Coordinator on this study.

Lastly, SenseHealth has changed its name to Wellpass and the TRC has moved its location to 3535 Market Street

At the time of this amendment, the following number of subjects have been randomized at the following sites:

CMCVAMC: 42
Pittsburgh VA: 3
University of Pennsylvania: 6

1.1 Explain if and how the follow-up of subjects will occur. **Research follow up visits will occur at 3, 6, 9, 12, and 18 months post baseline. For participants enrolled after 4/1/2019 research follow up visits will occur at 3, 6, 9, and 12 months post baseline. Participants will complete a locator form at baseline to assist the study team in scheduling future research visits. Subjects can fill out as much or as little of this form as they want to.**

1.2 Describe where, how and who will be conducting study procedures. **Research staff will administer the questionnaires, interviews, and collect urine samples from participants. CMCVAMC lab staff will collect blood.**

1.4. If a survey study, specify the estimated amount of time that subjects will need to complete the questionnaires/tools. **Baseline assessments will take approximately 2.5 hours and follow up visits will take approximately 1.5 hours.**

1.5. If a blood draw, specify the amount of blood to be drawn in milliliters and in teaspoonfuls or tablespoonfuls and specify how often and where the blood will be drawn. **Blood will be drawn in the CMCVAMC lab on the third floor by CMCVAMC lab staff. Two tubes of blood (4 teaspoons or 20 mL) will be collected, one tube (2 teaspoons) for disialo carbohydrate-deficient transferrin (%dCDT) testing and the other (2 teaspoons) for gamma-glutamyl transferase (GGT) testing. The CMCVAMC lab will conduct the GGT testing. The second tube of blood will be centrifuged and have the serum extracted by the TRC (Treatment Research Center) at the University of Pennsylvania who will then prepare the serum for shipping to the MUSC for the %dCDT testing.**

2. **Data Collection** (Include all questionnaires and survey tools with the submission.)

2.1. Provide

2.1.1. the mode of data collection, e.g. telephone, in-person, questionnaire, interviews, **Data will be collected via paper and stored in locked cabinets in MIRECC., and by direct data entry into the intranet web-based system housed on the CMCVAMC server. It will be set up on the CMCVAMC server (https://vhaphimulhl2.v04.med.va.gov/dmumain/), and accessed through the CMCVAMC intranet)**

2.1.2. the precise plan for how data is to be collected or acquired **Data will be collected in a private location by research staff. Data collected via paper will be entered into the computer by a research technician, coordinator, counselor, or clinical liaison. Data collected directly onto the computer will be reviewed by the research staff. The data will be identified using a four digit subject id number. Subject ID numbers are generated from order enrolled in the study, starting with 1001.**

2.1.3. exact location where data will be collected, **MIRECC interview rooms, 2nd floor**

2.1.4. exact location where data entry will take place. **MIRECC interview rooms, 2nd floor.**

2.1.5. the "title" of individual(s) collecting the data and analyzing the data, e.g. principal investigator, research coordinator. **PI, co-investigator, research coordinator, research technicians, data analyst**

2.2. Provide a time line for each aspect of the study. **In the first six months of funding, we will accomplish the following tasks.**

- **First, we will complete work with Dr. Muench and Wellpass to prepare the text-messaging system for the study, and finalize all manuals for the prevention intervention (PI). Dr. Muench serves as a consultant for**

Wellpass during the creation of the content of the study's text messages. He will not have access to other data regarding text messages or information provided by Veterans.

- **Second, we will pilot test methods to identify Veterans with chronic pain who are receiving daily opioid medication through CMCVAMC pharmacy records, and the screening procedures to detect risky alcohol use in these individuals.**
- **Third, we will complete training for the two research counselors in PI, and identify and begin training a third research counselor. Enrollment of study participants will commence in month 7 and will be completed by the end of Y3, based on a conservative recruitment rate of 10 participants per month. Given the 18-month follow-up period, all follow-ups will be completed by month 6 of Y5, which would leave 6 months to complete and submit the main outcome papers.**

2.3. Chart/Records/Data Review (retrospective and/or prospective)

2.3.1. Provide the planned or approximate number of charts/records/data to be accessed

2.3.1.1. CMCVAMC

2.3.1.2. Other site

2.3.2. Does this protocol employ an Honest Broker? ☐YES ☒NO

2.3.2.1. If yes, provide name of individual.

2.3.2.2. If no, explain who will access the charts/records.

2.3.2.3. Describe from what database charts/records/data will be accessed.

3. **Future Use of Data and Re-Contact**, if applicable. **N/A**

3.1. If any of the participant's data are going to be retained after the study for future research, the following information must be provided to the participant:

3.1.1. Where will the data be stored?

3.1.2. Who will have access to the data?

3.2. If the subject is going to be re-contacted in the future about participating in future research, this must be specified. Describe the circumstances under which the participant would be re-contacted whether within the VA or outside the VA.

3.2.1. If subjects will receive aggregate study results at the end of the study, the informed consent document must contain this information.

4. **Specimen Collection**

4.1. Give the source of all specimens and whether they were collected for research, treatment or diagnosis. **Blood and urine will be collected for research purposes and will be labeled with Subject code and date sample was collected. Results from both the urine and blood tests will not be part of the subject's electronic CPRS medical record.**

4.2. State where specimens will be stored, secured and when discarded. **Urine will be stored, tested, and discarded as per the CMCVAMC lab protocol. Blood to be tested for GGT will be stored, tested, and discarded as per the CMCVAMC lab protocol. Blood to be tested for %dCDT will be walked from the CMCVAMC lab to the Treatment Research Center (TRC) lab at the University of Pennsylvania, 3535 Market Street, where it will be centrifuged and the serum extracted. The serum will be stored until enough samples are collected to send to the Medical University of South Carolina (MUSC).**

4.3. Explain how destruction of samples will be substantiated. **MUSC will provide notification of the destruction of samples.**

P. **Genetic Testing, if applicable**

1. Explain if the study is looking for an association between a genetic marker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value.

   1.1. The uncertainty regarding the predictive value of the genetic marker is such that studies in this category will not involve participant counseling.
   1.2. Describe if the study is based on the premise that a link between a genetic marker and a specific disease or condition is such that the marker is clinically useful in predicting the development of that specific disease or condition.
   1.3. Will the subject be notified of the results and the provision for genetic counseling?
   ☐ Yes ☐ No ☒ N/A
      1.3.1. If yes, explain further.
   1.4. If biological specimens are used in this protocol, please respond to the following questions by checking the appropriate box:

	YES	NO	N/A
a. Does the project involve genetic testing?	☐	☒	☐
b. Will specimens be kept for future, unspecified use?	☐	☒	☐
c. Will samples be made anonymous to maintain confidentiality? *(Instructions: Note: If there is a link, it is not anonymous. Coding is not anonymous.*	☐	☒	☐
d. Will specimens be destroyed after the project-specific use is completed?	☒	☐	☐
e. Will specimens be sold in the future?	☐	☒	☐
f. Will subjects be paid for their specimens now or in the future?	☐	☒	☐
g. Will subjects be informed of the results of the specimen testing?	☒	☐	☐
h. Are there any implications for family members based on specimen testing results? (If yes, they may be participants.)	☐	☒	☐
i. Will subjects be informed of results obtained from their DNA?	☐	☐	☒

   1.5. Will specimens be de-identified? ☐YES ☒NO ☐ N/A
      1.5.1. If yes, please describe the procedures to be used.
      1.5.2. Include at what point in the process the specimens will be de-identified.
   1.6. Describe what measures will be taken to minimize the following risks from breaches of confidentiality and privacy resulting from participating in **THIS aspect** of the research project:
      1.6.1. physical
      1.6.2. psychological
      1.6.3. financial
      1.6.4. social
      1.6.5. legal harm

Q. **Banking of Collected Specimens**

1. **Will collected specimens be banked**? ☐YES ☒NO ☐N/A
   1.1. *IF BANKING SPECIMENS, IT MUST BE AT AN APPROVED VA REPOSITORY*. (*For additional information, contact the IRB office.)*
   1.2. If yes, specify the location where specimens will be banked.
   1.3. Explain how destruction of banked samples will be substantiated.

R. **Subject Recruitment** (characteristics of the study population)

1. **Provide the planned or targeted enrollment at**:
   1.1. CMCVAMC - **115 (90 undergoing treatment and 25 just being followed and not undergoing one of the treatment groups)**
   1.2. Other sites - **60 (10 at VA Pittsburgh; 50 at Penn)**
   1.3. Not applicable; chart review or use of previously collected data - ☐

2. **Screening and/or Eligibility Requirements - Inclusion/exclusion criteria are the same for screening before and after consent, however, some assessments used to determine final eligibility (such as the SCID and the MINI) are only administered once the Veteran comes to the lab (which occurs after a positive phone screen)**

2.1. Describe and provide justification for:

2.1.1. Inclusion criteria: **To be eligible for participation, Veterans must: (1) currently be receiving daily treatment with a prescription opioid for chronic pain, OR receive a daily prescription for opiate replacement therapy and have a chronic pain diagnosis; (2) be between the ages of 18 and 75; (3) have a cell phone capable of receiving text messages; (4) and be willing to be in a study where they might receive text messages.**

If at some point during follow-up research visit, if a subject admits to drinking they will move on to the treatment arm that they were randomized to upon entry into the study.

2.1.2. Exclusion criteria: **Veterans will not be eligible if they: (1) meet DSM-V criteria for a moderate to severe alcohol or drug disorder (with the exception of nicotine abuse/dependence); (2) have a current psychotic disorder severe enough to require inpatient treatment; or (3) are participating in alcohol use treatment at the VA or elsewhere (with exception of screening and brief intervention at the VA); (4) are currently on palliative care or are being treated with opioids for cancer-related pain.**

2.2. List all screening and/or eligibility requirements. **To be eligible for participation, Veterans must: (1) currently be receiving daily treatment with a prescription opioid for chronic pain OR receive a daily prescription for opiate replacement therapy and have a chronic pain diagnosis; (2) be between the ages of 18 and 75; (3) have a cell phone capable of receiving text messages; (4) and be willing to be in a study where they might receive text messages. Veterans will not be eligible if they: (1) meet DSM-V criteria for a moderate to severe alcohol use disorder (with the exception of nicotine abuse/dependence); (2) have a current psychotic disorder severe enough to require inpatient treatment; (3) are participating in AUD treatment at the VA or elsewhere (with exception of screening and brief intervention at the VA); or (4) are currently on palliative care or are being treated with opioids for cancer-related pain.**

2.3. Explain any special test or evaluations potential subjects may have to undergo before they are actually determined to be eligible for the study. **The SCID and MINI will be administered to ensure that potential subjects do not meet DSM criteria for moderate to severe alcohol or drug disorders (except nicotine) or have a current psychotic disorder severe enough to require inpatient treatment. If this is found during the research, we will refer the patient via a "warm hand-off" to either Dr. Oslin, co-investigator, or Dr. DePhilippis, clinical liaison.**

2.4. Not Applicable; subjects not recruited; chart review. ☐

3. **If applicable, indicate what populations will be targeted for recruitment as participants. Check all that apply.**

Males	☐
Females	☐
Inpatients	☐
Outpatients	☒
VA Employees	☐

Non-English Speaking**	☐
Veteran Family members***	☐
Non-Veterans***	☐
Other (Specify)	☐
Not Applicable, chart review	☐

3.1. **For non-English speaking subjects - If an investigator proposes to use a participant population that does not speak or read English, a copy of the translated document, as well as the English version, needs to be forwarded to the IRB for approval. Translator certification is also required.

3.2. ***If non-Veterans will be recruited for this study, explain why sufficient Veterans are not available to participate in the project [VHA Handbook 1200.5, paragraph 16a]. Veteran's spouses/partners, caregivers, etc. are considered non-Veterans for the purposes of this study.

3.3. ***Has approval to recruit non-Veterans been received from the ACOS/R&D and Medical Center Director?

3.3.1. ☐ Not Applicable

3.3.2. ☐ Pending *(Non-Veteran forms should be used. IRB office will obtain approval from ACOS/R&D and Medical Center Director.)*

4. **Does this project target a specific race or ethnic group as participants?** ☐YES ☒ NO

If yes, check all that apply.

Race	
American Indian or Alaskan Native	☐
Asian	☐
Black or African American	☐
Native Hawaiian or other Pacific Islander	☐
Black, not of Hispanic origin	☐
White, not of Hispanic origin	☐
Other	☐

Ethnicity	
Hispanic or Latino	☐
Not Hispanic or Latino	☐
Other	☐

4.1. Provide justification why this/these group(s) was/were chosen.

5. **What is the age range of participants?** Check all that apply.

Children (Under 18) Requires Waiver from CRADO (VHA Directive 2001-028, Research Involving Children)	☐
Young Adults (18-21)	☒
Adults (22-65)	☒
Seniors (Over 65)	☒
Over 89	☐
Not Applicable, chart review	☐

6. **Are there specific reasons why certain populations (i.e., age, gender or ethnic groups) are excluded as participants?** ☐YES ☐NO ☒N/A

6.1. If yes, specify reasons.

7. **Does the project require enrollment of the following classes of participants?**

	YES	NO
a. Employees	☐	☒
b. Individuals with impaired decision making capability	☐	☒
c. Pregnant women	☐	☒
d. Economically and/or educationally disadvantaged persons	☐	☒
e. Prisoners	☐	☒
f. Illiterate, limited, or no English language proficiency	☐	☒
g. Terminally ill patients	☐	☒

7.1. If applicable, what is the justification for including any of the above classes of participants in the project?
7.2. If the project requires enrolling any of the above classes of participants describe any project-specific measures or special considerations, steps, or safeguards to ensure that these individuals are adequately protected.

8. Describe the exact plan how subjects will be identified and recruited for the study. **Refer to procedures section for details about recruitment.**

9. Discuss methods, e.g., referrals from physician offices, clinics, programs, or through advertisements and brochures. **We will be using VISTA records to identify Veterans on daily opioids. We will notify their prescribing physician in order to contact the Veteran about the study. We will then send a letter to the Veteran telling the Veteran about the study. We will also accept referrals from the BHL.**
   9.1. If using a clinic, be specific about who will identify the potential subject and how that information will be transmitted to the research staff.
   9.2. If snowball method will be used, discuss the process and how the first individuals will be recruited. **n/a**
   9.3. Describe how information will be disseminated to subjects, e.g. handouts, brochures, flyers and advertisements *(include all recruitment materials with this submission)*. **Potential participants will be sent a letter about the study. We will then follow the letter up with a telephone call. Because we are concerned that when we state the full name of the study, Veterans would worry that we are trying to take their opiate prescriptions away due to alcohol use, we do not include the title of the research project in the letter or phone calls. We state only that it is a research project for Veterans prescribed opiates for chronic pain.**
   9.4. **Non-Veteran participants will be given a copy of the Notice of Privacy Practices.**

NOTE:
- *Every non-Veteran should sign VA form 10-0483, Acknowledgement of the Notice of Privacy Practices (ANOP)*
- *Once the ANOP is signed, the research study staff must send the non-Veteran's name to the CMCVAMC Privacy Officer via encrypted e-mail. The signed ANOP must be kept in the research study binder.*
- *If an oral informed consent is used, the NOP should be sent to the non-Veteran via postal mail. In addition, the research study staff must write a Note-to-File that the NOP was sent to the non-Veteran.*

10. **Informed Consent**
   10.1. Informed Consent will not be sought. ☐
   10.2. Written informed consent from participants. ☒
   10.3. Written informed consent from participants' legally authorized representative (LAR) as required by VA policy and/or applicable state laws. ☐
   10.4. Request Waiver of Documentation of Informed Consent ☐
   10.5. List the **title** of the key personnel involved in the following activities:
      10.5.1. **Person Obtaining Consent**
         10.5.1.1. Provide the title(s) of individual(s) **Research Coordinator, Research Technician, Research Counselor, Co-investigator and clinical liaison.**
         10.5.1.2. Type of training received to perform this process **HIPAA, CITI, Human Subjects, and consent training from PI.**
      10.5.2. **Pre-Recruitment Screening** (the use of medical records and other data bases to determine populations and individuals eligible for the study), **Research Coordinator, Research Technician, Research Counselor**

10.5.3. **Recruitment Process** (the process in which individuals are contacted and first introduced to the study and to the possibility of participating as subjects), **Research Coordinator, Research Technician, Research Counselor**

10.5.4. **Informed Consent Process** (the process by which recruited subjects are fully informed about participating in the study and then formally give their voluntary consent for participating), **Research Coordinator, Research Technician, Research Counselor**

10.5.5. **Screening of Recruited Subjects** (those activities in the protocol in which a final determination of eligibility of prospective subjects is made during the early phases of the study, using laboratory data, inclusion and exclusion criteria, and other person-specific information), **Research Coordinator, Research Technician, Research Counselor**

10.5.6. Include the breakdown of each individual's responsibilities:

10.5.6.1. Principal Investigator, **Monitor data and patient safety, ensure adequate training of personnel, review SAEs.**

10.5.6.2. Co-Principal Investigator, **train research counselors on integrating intervention notes into CPRS and communicate with providers in the system, review SAEs in the absence of the PI, provide clinical assistance if a participant starts to decompensate in a research visit or if a patient reveals they are a threat to themselves or others. Co-investigator will also help obtain consent.**

10.5.6.3. Research Coordinator, **ensure appropriate procedures are being followed for recruitment and consenting process, keep regulatory binder up to date; monitor accuracy of data collected and communicate with PI if there are any problems, communicate with IRB, recruitment, consenting, send informed consents and HIPAA authorizations to HIMS for scanning of documents, complete research visits.**

10.5.6.4. Additional research staff by title,
Research Technicians – recruit, consent, send informed consents and HIPAA authorizations to HIMS for scanning of documents, perform research visits, schedule follow ups.

Research Counselors – Recruit, consent, complete initial research visits (baseline), provide assessment, brief interventions, telephone monitoring and counseling phone calls, and monitor text messages.

The clinical liaison will be monitoring the phone calls made by the research counselors to ensure adherence to the manual. Additionally, the clinical liaison will be able to obtain consent in the event the two research technicians are unavailable. The clinical liaison will also have the authority to refer participants to the ARU (alcohol response unit) for a higher level of care, if needed.

Our research counselors are Masters level clinicians trained in recovery counseling and the administration of Brief Interventions. Our counselors received their training on how to administer a BI from clinicians within the BHL.

10.6. Will informed consent be obtained from potential subjects prior to determining eligibility?
☐YES ☒NO ☐N/A

10.6.1. If no, provide justification and a HIPAA Waiver of Individual Authorization for Disclosure of Protected Health Information. **We will be using pharmacy**

records to identify Veterans who are prescribed opioids for chronic pain. This will be done prior to obtaining consent. Potential participants will answer screening questions prior to consent. This is a tool used in the clinics that we will use as an initial screening tool. The results of the screening will be coded to safeguard each Veteran's PII/PHI. A spreadsheet located on our secured study drive will be used to pair Veteran data to the code. Potentially eligible participants who then sign a consent form will undergo more in-depth screening to determine eligibility for randomization.

10.7. Define when a subject is enrolled into the study, e.g. after the subject signs the informed consent or after randomized to treatment. **A subject is enrolled once they have been randomized.**

10.8. Describe:

10.8.1. The process when informed consent will be obtained and protecting patients' privacy. **Consent will be obtained at the first research visit.**

10.8.2. Any waiting period between informing the prospective participant and obtaining consent. **The Veteran will be told of the study via letter. After the letter is sent potential subjects will receive a telephone call. However, obtaining consent will not occur until after the Veteran completes the VA's standard alcohol assessment and some other screening questions over the phone.**

10.8.3. Steps taken to minimize the possibility of coercion or undue influence. **Veterans will be explained clearly as to what is standard of care and what is research. They will be reminded over and over that research is voluntary. The consent will be reviewed at each research follow up visit as consenting is a process and not a one-time event.**

10.9. Provide the language

10.9.1. used by those obtaining consent **The language suggested by the VA consent template will be used.**

10.9.2. understood by the prospective participant or the legally authorized representative **It is assumed that the reading level understood by the population is 8th grade as that is considered the average reading level understood by Americans.**

10.10. Provide location where informed consent will be obtained. **MIRECC interview rooms.**

11. **Waiver or Alteration of Informed Consent Requirements/Waiver of Requirement to Obtain Documentation of Informed Consent**

11.1. Are you requesting a waiver or alteration of informed consent? *(Check all that apply)*

11.1.1. No ☐

11.1.2. Yes; provide justification. ☐

11.1.3. Yes; for recruitment purposes only. ☒

11.2. **Are you requesting a waiver to obtain documentation of informed consent?**

11.2.1. No ☒

11.2.2. Yes; provide justification. ☐

S. **Compensation** *(The amount of compensation may not constitute an undue inducement to participate in the research.)*

1. Summarize any financial compensation that will be offered to subjects. **Veterans that complete the baseline assessment prior to 4/1/2019 will be compensated $75, then $50 for each follow up research visit completed. Veterans that complete the baseline assessment after 4/1/2019 will be compensated $75 for the baseline visit, then $50 for the follow up research visits at 3, 6, and 9 months, then $75 for the final 12 month research follow up visit.**

2. Provide the schedule for compensation. **Veterans that complete the baseline assessment will be compensated $75, then $50 for each follow up research visit completed (3 month, 6 month, 9 month, 12 month, and 18 month). Veterans who are enrolled after 4/1/2019 will be compensated $75 for the baseline visit, then $50 for the follow up research visits at 3, 6, and 9 months, then $75 for the final 12 month research follow up visit.**
   2.1. Per study visit or session. **$50 to $75 as described.**
   2.2. Total amount for entire participation. **$325 for participants enrolled prior to 4/1/2019; $300 for participants enrolled after 4/1/2019**

3. Explain how compensation will be provided via cash, voucher, gift card, etc. **Participants will be paid with the Greenphire ClinCard system. Participants will receive a card like a debit card (called a ClinCard), and money will be added after each study visit by study staff. Funds added to the card should be available immediately, however in some cases it may take 1 business day. The Veterans will sign and date a receipt when they receive the ClinCard that details how much they were compensated and that it was for research. Details of the research participation are not included in order to protect Veteran privacy. The receipt also does not contain mention that the participant was a Veteran. A copy of the receipt will be kept in the MIRECC office. The original paper copy will be secured in a locked cabinet in the PI's offices at 3535 Market Street. The cabinets reside in a locked room, and entry to the offices is restricted by an ID card scanner. Another copy of the receipt will be sent to the Penn Office of the Treasurer, where it will be secured in a locked cabinet.**

4. If financial compensation will be prorated, explain the process. **Subjects will be paid after each completed assessment**

5. Not Applicable - ☐

T. **Withdrawal/Early Withdrawal**

1. Describe how and when a subject may withdrawal from the study. **A participant may withdraw at any time by simply indicating to anyone in the research team that they no longer wish to participate. Subjects will be provided with the Revocation of HIPAA Authorization form.**

2. Provide procedures for the orderly termination of participation by the participant and if any consequences would result from early withdrawal from the study. **Upon the participant informing us they no longer wish to participate, they will be removed from active status on the study. There are no consequences to early withdrawal.**

3. Explain if survival data is required. If so, clarify how data will be obtained. **N/A**

4. Not Applicable; subjects not recruited; chart review. ☐

U. **Risk/Benefit Assessment**

1. **Potential Study Risk**s
   1.1. Describe and assess all of the following risks that may be associated with the research:
      1.1.1. Physical **There is a small chance of mild pain and swelling where the needle enters the skin and vein, bruising, infection and possibly fainting during the blood draws at baseline and 18 months. Texting (reading and sending) while driving may potentially lead to automobile accidents and bodily injury.**
      1.1.2. Psychological **There is a small chance that talking about their personal history can be embarrassing and/or lead to psychological discomfort.**
      1.1.3. Social **There is slight risk of embarrassment in terms of coming to the MIRECC suite for the research as MIRECC is geared towards research with mental illness and the stigma associated with mental illness.**

1.1.4. Economic **There is no foreseeable economic risk to participation.**
1.1.5. Monetary **The Veteran will not have to pay for treatment or participation but will need to pay for transportation to get to the research visits.**
1.1.6. Legal **There is no foreseeable legal risk associated with the research. In Pennsylvania it is illegal to text while driving.**
1.1.7. Loss of confidentiality **In all research, indeed in all situations, there is a risk of a loss of confidentiality. For instance, if the participant does not have a password on their phone, anyone could pick up their phone and be able to read their confidential messages. This is of incredible importance to the research team and confidentiality will be closely guarded. We will guard participants' information through secure servers (for web-based data) and in locked cabinets in with the MIRECC suite (for paper-based data). In addition, there is the risk that a person authorized to access the text messages might use them for an unauthorized purpose or disclose them to an unauthorized party.**
1.1.8. Assess the likelihood and seriousness of such risks. **Low.**
1.1.9. Other **N/A**

1.2. Specify what steps will be taken to minimize these risks. **Research staff is trained in the proper use and storage of confidential information as well as not to disclose information over the phone. Research staff is also trained in proper interviewing methods and how to handle delicate questions (such as questions regarding PTSD, etc). We have clinicians on hand at the VA who can speak with any Veteran who has experienced discomfort as a result of the research visit. We will attempt to schedule research visits on days that the Veteran has another appointment scheduled to minimize travel costs. Participants will be reminded of the risk of texting while driving and will affirm that they will not engage in this behavior with their signature on the consent form.**

1.3. If methods of research create potential risks, describe other methods, if any, that were considered and why they will not be used.

1.4. If chart review, breach of confidentiality is always a concern. Specify what steps will be taken to minimize these risks.

2. **Potential Study Benefits**

2.1. Assess the potential benefits to be gained by the individual subject, as well as benefits that may accrue to society in general as a result of the planned work. **The project will yield considerable information on whether a prevention intervention can help Veterans who are receiving prescription opioids daily and engaging in risky drinking reduce their drinking to below risky levels and sustain those improvements for 18 months. Information will also be obtained regarding moderators and mediators of intervention effects that are obtained. This information will be of direct value to VA treatment providers who are working with Veterans on prescription opioids and trying to reduce their risk for poor outcomes. Ultimately, the availability of effective prevention interventions will benefit Veterans on prescription opioids who are engaging in risky drinking.**

2.2. If the subject does not receive any direct benefit, then it must be stated here and in the consent form. **The subject may not receive any direct benefit from the study.**

3. **Alternate Procedures**

3.1 Describe the alternatives available to the subject outside the research context. **The alternative is VA's usual care which includes a brief intervention aimed at reducing drinking.**

3.2 If none, state that the alternative is not to take part in this research study at all.

V. **Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) (**All Phase III studies are required to have a DSMB. *However, the IRB has the right to require a DSMB with any study.)*

1. **Will an independent DSMB or DMC oversee the project?** ☐YES ☒NO ☐N/A

2.1. If yes, please provide contact information for the DSMB or DMC or Coordinating Center Representative and attach a copy of the charter.

Name: Phone Number:
Title: E-mail**:**

2. **If a DSMB or DMC will not monitor this study, who will monitor this study? Check all that apply.**

☒ Principal Investigator
☐ Sponsor
☐ VA Cooperative Studies Program
☐ Safety monitoring committee

W. **Data Monitoring** (*Monitoring plans describe how a monitor, independent of the study team, regularly inspects study records to ensure the study is adhering to the study protocol and applicable research regulations and CMCVAMC requirements. Monitoring plans do not necessarily require the use of an independent Data and Safety Monitoring Board (DSMB). Such independent boards are usually reserved for high-risk phase I studies, or large, multi-center phase III trials. Federally funded studies may require the use of an independent DSMB.)*

1. **Describe the data monitoring plan.** (All protocols must have a data monitoring plan appropriate for the potential risks and the complexity of the study.) **Data will be collected using standardized forms and will only be identified with the study's ID of the participant. The codes that link the name of the participant and the study ID will be kept confidential by the project coordinator in a secured cabinet at CMCVAMC. Most of the study data will be entered directly into databases as it is collected, via an intranet-based data entry system at the CMCVAMC. Data forms that are not amenable to web-based data entry will be entered by the research staff, and discrepancies will be corrected by a supervisor, based on source documents. The quality of the data will be monitored once per month. The study's statistician will analyze the data, using SAS and SPSS software.**

The primary outcome measure will be rates of risky drinking (i.e., more than 4 drinks at any one sitting or more than 14 drinks/week for men; more than 2 drinks at any one sitting or more than 7 drinks/week for women) within each follow-up period (e.g., months 1-3, 4-6, 7-9, 10-12, 13-18), as determine by the TLFB. Secondary outcomes in the study will be self-reported frequency of heavy drinking days (TLFB), biological measures of alcohol use ((%dCDT and GGT), urine toxicology tests to assess other drug use, VA medical records of opioid overdoses, depression, and pain. Outcome data will be analyzed using mixed effect regressions for continuous and categorical data (i.e., SAS) and various packages to examine mediation effects (i.e., MPlus). The alpha level for the primary outcome will be set at 5%.

Data quality will be monitored by random inspection of the completed forms by the research coordinator and any problems detected will be discussed with the PI. The Research prevention counselors will receive standardized training on the interventions, which are all manualized. Adherence to the manuals will be monitored using audiotapes and individual supervision provided by the clinical coordinator. If drift is observed the counselors will be re-trained.

Blind interim analyses of the data will be conducted at two points when 50 and 75% of the sample has been accrued. If the results show statistically overwhelming significant differences between groups, the study will be stopped (or one of the conditions stopped).

2. **Describe how protocol deviations, adverse events, serious adverse events, breaches of confidentiality, unanticipated adverse device effect (UADE), and unanticipated or unexpected problems will be reported to the CMCVAMC IRB and sponsor**. *(Refer to the CMCVAMC IRB Standard Operating Procedure (SOP) Manual for reporting guidelines.)* **In this study we will use the FDA definition of serious adverse events (SAEs). SAEs will be systematically assessed at each clinic visit. Any SAE, whether or not related to study intervention, will be reported to the IRB and DoD. The initial SAE report will be followed by submission of a completed SAE report to both institutions. In the event that a participant either withdraws from the study or the investigator decides to discontinue a participant due to SAE, the participant will be monitored by the investigator via ongoing status assessment until either a resolution is reached (i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected), the SAE is determined to be clearly unrelated to the study intervention, or the SAE results in death. Unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study and all volunteer deaths related to participation in the study should be promptly reported by phone (301-619-2165), by e-mail (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the U.S. Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office. A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RPH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.**

   Additionally, SAE's, protocol deviations, breaches of confidentiality and unanticipated or unexpected problems will be reported to the VA IRB within five days of discovery.

   2.1. Describe the management of information obtain that might be relevant to participant protections such as:
      2.1.1. Unanticipated problems involving risks to subjects or others – **These will be reported to IRB within five days of discovery just as SAEs.**
      2.1.2. Interim results – **Will be report these at continuing review**.
      2.1.3. Protocol modifications – **Will be proposed to the IRB and practices will not change until the modifications are approved by the IRB**.

3. **If applicable, define the plan for subjects if research shows results such as:**
   3.1. Depression **If depression appears to be an issue for a participant, and they are not already receiving treatment, the research staff will consult with Dr. Oslin for a consult with the participant and a possible referral.**
   3.2. Suicide **Participants who indicate any suicidal ideation will be evaluated by Dr. Oslin, Dr. Kranzler, or Dr. DePhilippis at the CMCVAMC.**
   3.3. Abuse **It is anticipated that the Veterans in our study will be engaging in alcohol or drug abuse. Dr. Oslin will be consulted in the event there is significant change to the Veterans' use status. If the Veteran is in danger in terms of physical abuse or someone else is in danger due to the Veteran abusing them, Dr. Oslin will be consulted and the appropriate actions will be taken.**

4. **Statistical Analysis**
   4.1. Include statistical power calculations and the assumptions made in making these calculations. **We consider the primary hypothesis of risky alcohol use, which compares PI and BIO groups on five repeated binary outcomes. We use the sample size formulae of Diggle et al. We expect to have a 20% dropout rate by month 18, and to see a risky drinking rate of 30%. On the assumption of a within subject correlation of 0.3 (resp. 0.4, 0.5), our sample size of 150 per group provides 80% power for a main effect difference of 30% versus 20% (resp. 30% versus 19%, 30% versus 18%) for the BIO versus PI groups.**

March 2018 Amendment: Our original power analysis in the grant was very conservative, as it took into account multiple outcome measures and moderation and mediation analyses. We had our statistician re-run the analyses, focusing on the main effect treatment group comparison with the primary outcome measure. If we calculate sample size needed to have 80% power to find a 15- percentage point difference in rates of risky drinking between the two conditions (e.g., 35% control condition vs. 20% experimental condition on risky drinking rate), we need a total of 136 to 162 veterans (depending on different estimates of the correlation between the outcome measure at different follow-up points). If the effect is slightly larger (e.g., 20 percentage point difference), we only need 72 to 84 veterans in total. Therefore, with a combination of the new design we are confident that we will reach a sample size that will be sufficient to at least examine our primary outcome measure.

4.2. Define plans for data and statistical analysis, including key elements of the statistical plan, stopping rules and endpoints.

a. **Primary objective: The responses for the primary hypothesis comprise five repeated binary measurements per participant indicating risky alcohol use over the follow-up points. Our main analyses will use mixed effects logistic regression models to compare the two groups on the rates of risky alcohol use. We expect that linear and quadratic trends will account for the patterns of use across time. If residual analyses suggest significant lack of fit, we will examine more general time trends using spline specifications. The main explanatory variable will be a binary factor indicating intervention group, together with terms for time trends, and for group by time interactions, if appropriate. Based on analyses of similar data, we expect that a random intercept model, possibly with an autoregressive repeated measures structure, should provide a good fit to the covariance structure of the repeated measures, although we will examine more general specifications, if necessary. The estimated regression coefficients for the group variable, and possibly for group by time interactions, will address our primary hypothesis. We will test whether estimated coefficients are different from zero, and will report estimates and approximate 95% confidence intervals.**

b. **Secondary outcomes. For Hypothesis 1, we will use the same type of mixed effects logistic regression models as described above to compare the groups on urine toxicology tests for use of drugs other than alcohol. The frequency of heavy drinking is a count response, so we will use mixed effects Poisson regression models to compare two groups on the number of heavy drinking days in a week. The models will allow for over dispersion by including estimation of a variance inflation factor or, if this is insufficient, by considering mixed effects negative binomial regression models. Some subjects have more days without heavy drinking than would be expected under a Poisson model. To account for this, we will fit mixed effects zero inflation models. If levels of heavy drinking are too low even for zero-inflation models, we will compare the intervention groups on the absence or presence of any heavy drinking days in a week, using mixed effects logistic regression models. Measures of depression and pain, and biological measures of alcohol use, will be continuously distributed, and will be compared across the groups using mixed effects linear regression models, after transformation of these responses to approximate normality. The explanatory variables, time trends, and covariance structure for these secondary analyses will be chosen as described for the primary hypothesis.**

We will follow a similar approach for testing Hypothesis 2, using data generated by electronic medical records to count the number of opioid overdoses for each participant through the course of the trial. We expect low rates of OD, so we will compare the groups on the rates of having an OD via a logistic regression model. If the numbers of OD are sufficiently high, we will compare the groups using Poisson or Negative Binomial models for the total number of OD per participant across the trial.

c. **Moderator analyses. We will address Hypothesis 3 using moderator analyses extending the analyses described above. The models will be extended to include the main effect of measures of high risk status, including higher prescription opioid doses, co-occurring benzodiazepine use, poor social support, and low readiness for change, together with the interaction effect of these terms with the intervention group factor. If the inclusion of a given interaction term in a model yields significantly better model fit, this provides evidence for moderation. Data plots and the estimated regression coefficients for the intervention, the moderator, and their interaction will explain the nature of the moderating effect.**

d. **Mediation analyses. We will address Hypothesis 4 through mediation analyses, with changes in readiness for change, self-efficacy, and coping as mediators. Here, we will follow the methods described in (105) First, to address the time course of these mediators separately from outcome, we will use the same mixed effects model approach described above. Second, to address whether these mediators predict later risky alcohol use, we will conduct a further series of mixed effects model analyses, using lagged versions of the mediator variables as time-varying covariates, together with the intervention and the other explanatory variables described above. We expect that the intervention effects on the mediators and on the outcomes will occur gradually over time, so we will use a latent growth curve mediation model to address the joint behavior across time. As suggested by MacKinnon, we will also examine the fit of other types of models, to obtain a more complete assessment of the intervention's direct and indirect effects on outcomes.**

e. **Missing values. The mixed effects models will provide valid estimates of treatment efficacy if the missing data meet the ignorable missingness assumption. We will conduct further analyses to assess the sensitivity of our inferences to possible violations of this assumption. First, we will use pattern mixture models (104), defining a categorical variable describing the main patterns of missing data, and including it as a main effect and interaction effect with intervention group in the modes for primary outcomes. Significant differences in the estimated intervention effects across levels of the pattern variable suggest one type of non-ignorable missingness. Second, shared parameter models (104) assume that the repeated responses and repeated binary indicators of missingness have possibly correlated random effects, and significant correlation indicates possible non-ignorability. Finally, semiparametric regression models (106) use inverse probability weighting to extend the validity of GEE models, and provide a different type of sensitivity analysis for the mixed effects models. All three approaches require certain model assumptions, so we will compare the results of the analyses over a range of such assumptions.**

X. **Privacy and Confidentiality** *(Privacy refers to persons and to their interest in controlling the access of others to themselves.) (Confidentiality refers to protecting information from unauthorized disclosure or intelligible interception.) (Investigator should contact the Privacy Officer for additional details.)*

1. **Indicate the type of data that will be received by the Principal Investigator. Check all that apply.**
   - 1.1. ☐ De-identified – Without any identifiers that could link the data to a specific participant. (Contact Privacy Officer for assistance. *If data is coded, it is not considered de-identified.)*
   - 1.2. ☒ Identified – Linked to a specific participant by identifiers sufficient to identify participants. (See HIPAA and Common Rule Criteria for list of identifiers.)
   - 1.3. ☒ Coded – Linked to a specific subject by a code rather than a direct identifier. If coded is checked, specify:
     - 1.3.1 Explain who will maintain the link or code. **The research coordinator will maintain the link/code. Codes will be assigned during the initial screening phone call. The spreadsheet linking Veteran data to the code will be located on our secure study drive. Thus all data collected from screening onward will be protected by the code.**
     - 1.3.2 Describe who will have access to the link or code. **Research staff will have access to the codes.**
     - 1.3.3 Provide exact details for how the data is coded. **Participants will have a subject identification number that is a four digit number. We will use numbers sequentially, beginning with 1001.**

2. **Does the project require the use of existing Protected Health Information (PHI) from a database, medical records, or research records?** ☒YES ☐NO ☐N/A
   - 2.1. If yes,
     - 2.1.1. Specify the source of the existing PHI **VISTA Pharmacy and MHA records. (The Mental Health Assistant (MHA) is a software package for VistA. MHA was developed to create an effective and efficient tool for mental health clinicians and their patients to use for the administration and scoring of assessment instruments and interviews that are not available elsewhere in CPRS or VistA)**
     - 2.1.2. Indicate the specific data elements/identifiers (e.g., name, address, phone numbers, etc.) on the below table. **Name, address, phone number, opiate prescription status.**
   - 2.2. If the study uses an existing database/data warehouse,
     - 2.2.1. Provide a description of the database/data warehouse.
     - 2.2.2. Make clear who is responsible for maintaining it.
     - 2.2.3. Cite any relevant Standard Operating Procedures (SOP) for the database/data warehouse.
     - 2.2.4. Provide a copy of the SOP.

3. **Will PHI be collected prior to obtaining informed consent?** ☒YES ☐NO ☐N/A
   - 3.1. If yes, complete and provide a HIPAA Waiver of Individual Authorization for Disclosure of Protected Health Information with this submission.

4. **HIPAA Identifiers - Indicate the PHI that will be collected from project participants directly or indirectly.**
   - 4.1. ☒ Name
   - 4.2. ☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census
   - 4.3. ☒ All elements of dates (except year) for dates directly related to an individual, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
     - 4.3.1. ☒ Birth Date ☐ Date of Death

4.3.2. ☐ Discharge date ☐ Admission date
4.3.3. ☒ Appointment Dates ☐ Other Dates (e.g. lab tests, x-rays, MRI, etc.)

4.4. ☒ Telephone numbers
4.5. ☐ Fax numbers
4.6. ☐ Electronic mail addresses
4.7. ☒ Social Security/Medical Record Number
4.8. ☐ Health plan beneficiary numbers
4.9. ☐ Account Numbers
4.10. ☐ Certificate/license numbers
4.11. ☐ Vehicle identifiers and serial numbers, including license plate numbers
4.12. ☐ Device identifiers and serial numbers
4.13. ☐ Web universal resource locators (URLS)
4.14. ☐ Internet protocol (IP) address numbers
4.15. ☒ Biometric identifiers, including fingerprints, voiceprints, audio recordings
4.16. ☐ Full-face photographic images and any comparable images
4.17. ☐ Any other unique identifying number, characteristic, or code
4.18. ☐ Personal and Family History
4.19. ☐ History and Physical Examination ☐ Progress Notes
4.20. ☐ Discharge Summary(ies) ☐ Photographs, videotapes, other images
4.21. ☐ X-Ray ☐ HIV (testing or infectious disease) records
4.22. ☒ Diagnostic/Laboratory tests ☐ Sickle cell anemia
4.23. ☒ Drug Abuse Information ☐ Behavioral Health notes
4.24. ☒ Alcoholism or Alcohol Use ☐ Operative Reports
4.25. ☐ Billing records ☒ Medication List
4.26. ☐ Health Summary Reports ☐ Anatomic Pathology Report
4.27. ☐ Other Records:

5. **Will participants be contacted from existing PHI?** ☒YES ☐NO ☐N/A
   5.1. If yes, clearly explain how participants will be contacted (NOTE: this would be the same information as listed under section R.8 identification and recruitment of subjects). **We will use VA VISTA pharmacy records to identify Veterans who are currently being prescribed daily opioid medication for the treatment of chronic pain. Veterans already in addiction treatment will then be excluded from the study. For the remaining patients, the prescribing physicians will be contacted, and notified of our intention to contact the patient to tell him/her about the research study. We will then contact patients via letter to describe the research study and follow-up with a telephone call to invite them to participate.**

   Most often, the BHL refers Veterans to the study team who are engaging in risky drinking, but without the symptomology or levels of consumption that would warrant a referral to a higher level of care, such as the ARU. If during the triage assessment the BHL software flags a Veteran for risky drinking, but not a referral to a higher level of care, then the technician will refer them to the study team.

6. Provide the titles of the exact individuals who will have access to the collected data. **PI, Research Coordinator, Research Technicians, Data Analyst, Co-Investigator, and Clinical Liaison**
   6.1. Explain why these individual will have access to this data. **The PI has access for data safety monitoring. The research coordinator will be collecting and monitoring the data for adherence/accuracy/safety. The Research Technicians will be collecting the data and answering any queries that come up.**

Y. **Information Security** (*Contact the Information Security Officer for additional assistance regarding confidentiality (storage/security) of research data.)*
   1. Provide the precise plan how data is to be collected or acquired (repeat the same information

as listed under "Data Collection" section of this form. **Data will be collected in a private location by research staff. Data collected via paper will be entered into the computer by the researcher. Data collected directly onto the computer will be reviewed by the research staff. The data will be identified using a four digit subject id number. Phone calls between study participants and research counselors will be recorded using a digital recorder. The audio files created from these recordings will be stored on the VA server (https://vhaphimulhl2.v04.med.va.gov/dmumain/).**

January 2016 amendment to change data storage location: Due to a system failure of the MIRECC DMU at the VA, an amendment to this ongoing protocol was made to change where data was stored (as detailed above and in below sections that describe data storage). This is being done with the input from the ISO and PO, and under the current PENN-VA MOU on data storage (even though there is a separate PENN component to our study). The need to use the DMU at Penn is critical because the DMU provides more oversight and protection over the safety and integrity of the data, being able to capture every entry and any changes made. It also keeps the data on a highly secured server to protect not only against hacking, but against catastrophic loss of data.

We will re-consent current subjects.

We also note that there was no data loss to due to the VA DMU failure.

July 2016 Amendment – An amendment to the protocol has been made to change the server back to the secure server at the VA. The reason for this is an issue with software and being able to get through the VA firewall for data entry.

2. Provide a listing of the exact research data that will be stored, including but not limited to signed, original informed consent and HIPAA authorization forms, case report forms, etc. **Consents, HIPAA authorization, CRFs, blood and urine results, recordings from counseling phone calls. Being entered into DMU will be: dates of research visits, responses to questionnaires and interviews, as well as urine specimen and blood test results.**

3. Indicate how project's research data (original and all copies) will be stored and provide corresponding security systems. **Consents will be kept in binders in locked cabinets within the MIRECC suite at CMCVAMC. Paper Case Report Forms will be kept in a locked drawer in a locked office separate from the consents. All data will be entered into a web-based data entry system on a VA server. In addition, if a Veteran is in the PI condition and has consented to audio recording of their counseling session, we will be using digital recorders to capture the call, and then we will save the audio files of the call to the server (https://vhaphimulhl2.v04.med.va.gov/dmumain/).**

4. Provide exact location where research data (original and all copies) will be stored and secured. **Data will be stored in the MIRECC Suite, 2nd floor of Bldg 2. Veteran contact data for follow up and tracking purposes will be kept on the research server "McKay – PI with Vets."**

5. Explain how data is to be transported or transmitted from one location to another. **Phone numbers and participant id numbers will be transmitted to Wellpass through their website (www.wellpass.com) which will be accessed using a secure CMCVAMC computer and network. Participant id numbers, serum samples, session dates, and blood test results will be transferred to/from MUSC via a password-protected spreadsheet on an encrypted USB device. Data stored on DMU can be entered from the location at which the data is collected. It is transmitted via internet portal.**

5.1. Informed Consent discloses PHI transported or transmitted off-site. ☒YES ☐NO ☐ N/A

5.2. HIPAA Authorization discloses entities to whom PHI will be transported or transmitted. ☒YES ☐NO ☐N/A

5.2.1. List all entities or individuals outside CMCVAMC to whom data is to be disclosed, and the justification for such disclosure and the authority**. Blood samples will be sent to MUSC for analysis and will be coded as well. Wellpass (the company that created the SMS text messaging portion of the intervention) will have PHI – telephone numbers – of people randomized to receive the intervention. The Greenphire ClinCard system collects and uses PHI to pay participants.**

5.3. If yes, list the exact data that will be transmitted. **Blood samples with session dates and times and subject ID numbers will be sent to MUSC. Wellpass will receive phone numbers in order to conduct the text messaging portion of the intervention.**

5.4. If yes, explain how data will be protected during transmission outside of CMCVAMC. **Data will be coded with a four digit number. The link to the code will remain at the VA and not used during data analysis**

5.5. Off-site, provide exact location **University of Pennsylvania, 3535 Market Street, Philadelphia, PA 19104; Medical University of South Carolina, 67 President Street, Charleston, SC 29425; Wellpass, 175 Varick Street, Floor 6, New York, NY; Greenphire, 1012 W. 8th Avenue, King of Prussia, PA, 19406 10014** (If off-site, attach at least one of the following.)

5.5.1. Data Use/Transfer Agreement ☐YES ☒NO ☐N/A

5.5.2. Off-Site Storage/Transfer of Research Data ☒YES ☐NO ☐N/A

5.5.3. Memorandum of Understanding ☐YES ☒NO ☐N/A

5.5.4. *(Note: VA data disclosed to a non-VA investigator at an academic affiliate for research purposes needs to be approved by the Under Secretary of Health or designee.)*

6. List who is to have access to the data and how they are to access it (anyone who has access to the data is responsible for its security). **PI, co-PI, research coordinator, research technician, research counselor, data analyst**

7. Describe who is to have access and be responsible for the security of the information (e.g., the Coordinating Center, the statistician, and PI who has ultimate responsibility). **PI, co-PI, research coordinator, research technician, research counselor, clinical liaison, data analyst**

8. Provide mechanisms used to account for the information. **There is an electronic record of changes to the data that is stored in the web-based CMCVAMC DMU system. The research coordinator will be responsible for the day-to-day keeping of the information.**

9. Give security measures that must be in place to protect individually identifiable information if collected or used. **PII will be kept locked at the MIRECC Suite, Building 2.**

10. How and to whom a suspected or confirmed loss of VA information is to be reported.

10.1. **The Investigator will notify the Information Security Officer, Privacy Officer, IRB, Associate Chief of Staff for Research and Research Compliance Officer within one hour of a suspected or confirmed loss of VA information.**

11. Identify any circumstances that may warrant special safeguards to protect the rights and welfare of subjects who are likely to be vulnerable including, but not limited to, those subjects who may be susceptible to coercion or undue influence, and describe appropriate actions to provide such safeguards. **N/A**

12. Electronic PHI will be stored on the following:
    12.1. CMCVAMC desktop computer with password protection and/or encryption. ☐YES ☒ NO ☐N/A
        12.1.1. If yes, identify where the desktop is located.
    12.2. CMCVAMC secure server. ☒YES ☐NO ☐N/A
        12.2.1. If yes, identify the CMCVAMC server. **MIRECC research server "McKay - PI with Vets" https://vhaphimulhl2.v04.med.va.gov/dmumain/**
        12.2.2. External drive that is password protected and/or encrypted. ☐YES ☒NO ☐N/A
            12.2.2.1. If yes, identify the external drive.
    12.3. Off-Site server ☒YES ☐NO ☐N/A (If off-site, attach at least one of the following.)
        12.3.1. Provide exact location and the name of the off-site server
        12.3.2. Data Use/Transfer Agreement ☐YES ☐NO ☒N/A
        12.3.3. Off-Site Storage/Transfer of Research Data ☒YES ☐NO ☐N/A
        12.3.4. Memorandum of Understanding ☐YES ☐NO ☐N/A

13. Explain how data is to be transported or transmitted from one location to another. **Phone numbers and participant id numbers will be transmitted to Wellpass via a password-protected spreadsheet on an encrypted USB device. Participant id numbers, serum samples, session dates, and blood test results will be transferred to/from MUSC via a password-protected spreadsheet on an encrypted USB device. Electronic research data will be transmitted to the VA server via a web-based data entry system on the VA's intranet.**

14. Informed Consent discloses PHI transported or transmitted off-site. ☒YES ☐NO ☐N/A

15. HIPAA Authorization discloses entities to whom PHI will be transported or transmitted. ☒YES ☐NO ☐N/A

16. List all entities or individuals outside CMCVAMC to whom data is to be disclosed, and the justification for such disclosure and the authority. **Blood samples will be sent to MUSC for analysis and will be coded as well. Wellpass (the company that created the SMS text messaging portion of the intervention) will also have PHI – telephone numbers – of people randomized to receive the intervention. The Greenphire ClinCard system collects and uses PHI to pay participants.**

17. Clarify what protection exists for a database. **The web-based DMU system is double password protected and on a secure VA server.**
    17.1. Data is stored:
        17.1.1. With identifiers - ☐YES ☒NO
        17.1.2. Coded - ☒YES ☐NO
        17.1.3. De-Identified - ☐YES ☒NO
        17.1.4. Provide the exact list of identifiers that will be stored. **Dates of research visits**

18. Describe the plan for protecting research data from improper use or disclosure. **All staff will be sufficiently trained on the proper use of data and how to guard against improper use or disclosure.**
    18.1. The Investigator must notify the Information Security Officer, Privacy Officer, IRB, Associate Chief of Staff for Research and Research Compliance Officer within one hour of the improper use or disclosure.

19. Is there a plan to apply for a Certificate of Confidentiality? ☐YES ☒NO ☐N/A

19.1. If yes, provide a copy of the certificate with this application or to the IRB Office as soon as received.

20. **Record Retention**:
    20.1. The required records, including the investigator's research records, must be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1). VHA Handbook 1200.05 §26.h
    20.2. Until a schedule for local research records is published, ALL records including identifiers must be retained." ORO/ORD Guidance on Informed Consent Form Modifications Addressing VA Record Retention Requirements (July 23, 2009)
    20.3. If there are additional procedures for record retention, explain further. **N/A**

Z. **Qualification of the Investigators**

1. Provide a description of the qualifications of each investigator/co-investigator and their specific role in the study.

James McKay, PhD, PI: Dr. James McKay is a Professor of Psychology in Psychiatry at the University of Pennsylvania. He is the Director of the Penn Center on the Continuum of Care in the Addictions, and the Director of the CMCVAMC Center of Excellence in Substance Abuse Treatment and Education (CESATE). Dr. McKay received a Ph.D. from Harvard University, and completed a clinical psychology internship at McLean Hospital and a postdoctoral fellowship in treatment outcome research at Brown University.

He is the recipient of an Independent Scientist (K02) Award from the NIDA, as well numerous research grants from NIDA and NIAAA, including a new NIAAA-funded Center on Adaptive Treatment for Alcoholism. He is also the author of "Treating Substance Use Disorders with Adaptive Continuing Care" (2009; American Psychological Association).

Dr. McKay's work has included evaluations of continuing care treatments for alcohol and cocaine use disorders, evaluations of the ASAM placement criteria, development of adaptive interventions for substance use disorders, and the identification of factors over time that predict relapse following substance abuse treatment.

His current research efforts are focused on the development and evaluation of flexible approaches to the management of addiction, which include the use of the telephone to provide extended continuing care and incorporate adaptive algorithms and the client's preferences in the selection of treatment interventions.

Dr. McKay's role in the study is as the ultimate responsible party that the research and intervention is done as described, that data integrity is upheld, and that the safety of participants is upheld. It is also the responsibility of the PI to ensure adequate personnel is working on the study and that each has adequate training to perform their duties.

David Oslin, MD, co-PI: Dr. David Oslin is Associate Professor of Psychiatry at the CMCVAMC and the University of Pennsylvania Medical Center. Dr. Oslin is the Director of the VISN 4 Mental Illness, Research, Education, and Clinical Center (MIRECC) and the Associate Chief of Staff for Behavioral Health at the CMCVAMC. The MIRECC and Behavioral Health Laboratory support research on comorbidity and integrated care, respectively, and facilitate a number of research projects for post-doctoral fellows and faculty. Dr. Oslin is the author of over 80 research publications and 31 chapters, books, or editorials.

Dr. Oslin's research interests include studies access to behavioral health intervention care, treatment outcomes for addictive disorders, and pharmacogenetics of addiction treatment.

Specific projects include an adaptive treatment study of naltrexone to develop strategies for maintenance treatment and for non-response to treatment.

Two studies examine endophenotypes associated with alcohol craving, subjective high and intoxication. Two other studies explore improving access to treatment for alcohol misuse with a focus on brief interventions and care management services.

Additionally, Dr. Oslin continues research on the implementation and dissemination of evidence based practices for integrating primary and mental health care.

For those participants who choose to allow research information to be entered into CPRS, Dr. Oslin will be responsible for training research counselors on integrating intervention notes into CPRS and communicate with providers in the system, review SAEs in the absence of the PI, and provide clinical assistance if a participant starts to decompensate in a research visit or if a patient reveals they are a threat to themselves or others.

2. If applicable, the Principal Investigator must identify a qualified clinician to be responsible for all study related healthcare decisions. **David Oslin, MD.**

3. PI should submit a current, dated CV with each new initial review.