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PROTOCOL

STUDY TITLE
Primary care intervention to reduce prescription opioid overdoses - Prescription Opioid Safety Trial (POST)

SPONSOR INFORMATION
VA HSR&D – IIR 13-322

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SPECIFIC AIMS

Effectively managing pain while minimizing adverse outcomes is a high priority of the Veterans Health Administration (VHA).[1] Opioids have been increasingly prescribed for pain;[2] in the VHA, preliminary analyses by our study team indicate that the proportion of patients prescribed opioids increased from 17.4% in 2001 to 24.1% in 2009, and the percent receiving at least 120 days supply or more approximately doubled. Opioid therapy has become a common modality of treatment for chronic pain specifically.[3]

Overdose and other adverse outcomes related to opioid use have also increased and represent a significant threat to the safety and quality of VHA pain care as well as a national public health concern.[4] The rate of prescription opioid overdose deaths increased 293% between 1999 and 2009 in the U.S.[5] Increases in opioid overdose deaths have been more gradual in VHA (see preliminary studies), but the rate of unintentional overdose is higher among VHA patients than in the general population.[6] Studies by our study team indicate that: 1) 66% of VHA patients who died of an opioid overdose had received opioids from a VHA provider prior to death; 2) VHA patients prescribed elevated opioid doses (≥ 20 morphine equivalent mg/day) have increased risk for opioid overdose; and, 3) 76.4% of VHA patients who die of an opioid overdose were seen in primary care in the year prior to death (see preliminary studies). Among Veterans of the recent conflicts in Iraq and Afghanistan, receiving opioids is associated with overdose, self-inflicted injuries, and violence-related injuries.[7]

Efforts are underway to change opioid prescribing behavior, but concurrent strategies are needed to address patient behaviors that increase opioid overdose risk. Overdoses result from a range of behaviors, including taking more than prescribed, using multiple substances with synergistic effects, and injecting/snorting crushed pills to get high. Factors such as having a mental health condition have been found to increase risk of overdose among Veterans receiving opioids for pain.[8] Given the range of risk behaviors and relevant patient factors, tailored opioid overdose risk reduction strategies are urgently needed. Motivational enhancement (ME) is an evidence-based strategy that uses tailoring to enact behavior change through improving self-efficacy and motivation.[9,10] Recent VHA initiatives to increase behavioral health providers in primary care, such as Primary Care-Mental Health Integration (PC-MHI), provide a clear opportunity to deliver ME interventions to the many patients treated for long-term pain in primary care. Although the impact of ME on overdose risk behavior is unknown, the use of an ME approach to reduce overdose risk behaviors is potentially well-suited to the context of long-term opioid pain care, when total and immediate discontinuation of opioid use is often unfeasible.

The proposed Prescription Opioid Safety Trial (POST) study will be a randomized controlled trial of a brief, tailored ME intervention that incorporates cognitive behavioral strategies to increase pain coping and is aimed at reducing patients' overdose risk behavior. The study will recruit 450 patients from primary care clinics at the VA Ann Arbor Healthcare System. Patients with long-term opioid use, defined as treatment for at least 84 days covered within the last 90 days, who are prescribed opioid doses of 20 morphine-equivalent mg/day or greater (an indicator of overdose risk[12]) will be screened and recruited into the study. Participants will then be randomized to either the intervention (n = 225) or an enhanced usual care (EUC) condition (n = 225); both conditions will be delivered by PC-MHI therapists. Pharmacy records and patient self-report will be assessed at baseline and 3-, 6-, and 12-month follow-ups to measure key outcomes. The **specific aims** are:

Aim 1) to examine if patients randomly assigned to a brief overdose prevention intervention report reduced overdose risk behaviors (e.g., higher dose, concurrent alcohol use, concurrent other drug/medication use, returning to normal dose after breaks in use) over one year of follow-up compared to patients assigned to equal attention EUC.

Aim 2) to examine if patients randomly assigned to a brief overdose prevention intervention have lower total quantities of opioids prescribed (from pharmacy fill records) and aberrant opioid use (e.g., using for reasons other than pain, obtaining opioids from someone other than primary provider) over one year of follow-up compared to patients assigned to equal attention EUC.

The study will include two **secondary aims: 1)** to examine if patients randomly assigned to the brief intervention have fewer non-fatal overdoses and other medication-related adverse events (emergency department visits, over-sedation, injuries), better functioning, and more often store and dispose of opioids safely compared to patients assigned to EUC; and **2)** to examine mediators (motivation and self-efficacy) and moderators (OIF/OEF/OND status, baseline mental health) of intervention effects.

The proposed POST study will increase our understanding of strategies to reduce adverse outcomes related to prescription opioid use, namely, risk of overdose, among VHA primary care patients. This study is the next logical step in addressing the risks of prescription opioid use among VHA patients, providing critical, initial data to inform VHA clinicians to prevent adverse opioid-related outcomes. Knowledge generated from

this pragmatic trial is likely to have broad implications for improving safe opioid use, the enhancement of PC-MHI services, and the quality of pain care for current and future VHA patients.

BACKGROUND

Context. Beginning in the early 2000's, opioid analgesic (OA) use increased sharply in the U.S. for the treatment of chronic non-cancer pain[2] in response to concerns about the under-treatment, guidelines recommending more extensive use of OAs, and the Joint Commission introducing pain as the "fifth vital sign."[13] Trends in OA prescribing have paralleled increases in adverse outcomes related to OAs, the most concerning of which is overdose. The rate of OA-specific overdoses increased by nearly 300% between 1999 and 2009[5], and OAs accounted for 57.6% of all overdose deaths in 2010.[14] There were an estimated 855,348 emergency department visits related to OAs in the U.S. in 2011, a 186% increase from 2004.[15] Consequently, strategies to improve the safety of OA therapy are critically needed.

OA therapy for pain and risk of adverse outcomes. Patients receiving OAs are at increased risk for adverse OA-related events. For example, in a study of Medicare health plan members, those patients treated with OAs for chronic pain had an average of 1.5 emergency department visits over one year, compared to 0.6 among other patients.[16] Many OA overdose decedents were receiving OAs for pain prior to death. In our study of VHA patients, 66.2% of OA overdose decedents had been prescribed an OA by a VHA provider prior to their death.[12] It is likely that many OA overdoses among Veterans could be prevented through interventions targeting patients prescribed OAs for pain in the VHA system.

OA Regimen. In our national study of VHA patients, we found a dose-response relationship between prescribed dose of OAs and risk of OA overdose death, with hazard ratios (HRs) of 1.9, 4.6, and 7.2 associated with 20 to < 50, 50 to <100, and 100+ morphine-equivalent mg (MEM)/day respectively (vs. 1 to <20 mg/day) among patients with chronic pain.[12] As a result, the VHA issued new recommendations to avoid doses above 100 MEM/day[17]; however, even moderate doses are associated with increased risk.[12] Regardless of whether these associations are causal or due to unmeasured confounding factors, these data indicate that moderate or greater prescribed dose of OA can be used as an indicator to identify those patients who are at increased risk for overdose and who may benefit from OA safety-focused interventions.

Patient Factors. In our study of VHA patients treated with OAs for chronic pain,[12] patients who had an injury/acute pain diagnosis, a substance use disorder, or other psychiatric disorder had a greater risk of unintentional overdose. Age less than 50 was also associated with OA overdose in this study, and although Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OIF/OEF/OND) status was not examined as an independent risk indicator, it is likely that these Veterans are at higher risk for overdose than other Veterans. In a study of service use among patients receiving OAs for chronic pain,[18] younger age, female gender, the number of other mental health conditions, and number of days supplied of a sedative or hypnotic medication were associated with emergency department utilization. Some evidence suggests that risk factors for overdose may tend to cluster; in a study of patients with lower back pain, patients receiving high doses of OAs were more likely to have a mental health or substance use condition or to have concurrent sedative use.[19]

Risky OA use. The term "Aberrant OA use" refers to use of OAs that is inconsistent with the prescribed regimen and that carries some risk. Aberrant OA-related behaviors vary widely. Although some behaviors likely indicate that opioids are no longer therapeutic, the behaviors that are more severe indicators of problems are relatively uncommon. In contrast, many less-severe behaviors are common among patients prescribed OAs. Overdose risk behaviors as a distinct group of behaviors from those typically measured as aberrant use in screening tools; some aberrant opioid use behaviors may co-occur with overdose risk behaviors, while others may not (*See Table 1*).

Table 1. **Examples (also see Measures section)**

Aberrant OA Use	Overdose Risk Behaviors
More than prescribed	High total dose consumed
Less than prescribed	Resumption of use after a break long enough to reduce tolerance
Getting OAs from friends or family or diverting	Using alone
OAs from multiple prescribers	Combining with other substances
Using for reasons other than pain (sleep, anxiety, get high)	Other routes of administration (injecting or snorting)

In a sample of Veterans treated for chronic non-cancer pain, 53% reported that they used more than prescribed at least occasionally.[20] Additionally, 30% of this sample reported that they had requested an early refill of an opioid at least once in the past year and 8% reported that they had borrowed pain medications from friends or family. In total, 79% of Veterans in this study endorsed at least one aberrant behavior. Thus, a substantial portion of Veterans receiving OAs for pain care use OAs in a manner that is inconsistent with the prescribed regimen and may benefit from interventions to identify and reduce those

behaviors that increase risk for overdose and other poor outcomes.

Non-VHA research further indicates that aberrant OA use is common among patients with chronic pain. In a study of individuals on long-term OA therapy, 79% had evidence of non-adherence based on urine drug screens.[16] Among those who were non-adherent, 47% had higher levels of OAs than expected, 41% had used non-prescribed controlled substances, and 12% had used illegal drugs. In a study of 904 patients treated for pain in primary care, 80.5% of participants reported at least one of twelve aberrant behaviors, although reaching the threshold of substance use disorder was unusual.[21] Consequently, although referral to specialty addictions treatment is an important clinical consideration in some cases, this level of care is likely not indicated for the majority of patients with aberrant, and potentially risky, OA use behaviors.

In the study of aberrant OA use behaviors among Veterans,[20] the only clinical or demographic characteristic that was significantly different between those patients who did and did not report aberrant use was major depressive disorder. This finding points to the potential importance of mental health, especially depression, in aberrant OA use among Veterans.

Stakeholder response. In light of the increases in adverse consequences related to OAs, stakeholders have undertaken a number of new initiatives. In 2011, the White House announced a plan to decrease unintentional OA overdose deaths by 15% in 60 months through provider and public education, expanding prescription drug monitoring systems, and increasing use of brief intervention protocols. In 2009, a review panel for the American Pain Society and the American Academy of Pain Medicine published recommendations on the use of OAs for chronic pain treatment in response to the increase in adverse consequences related to OA use.[22] The principal recommendation was for clinicians to assess risk for adverse outcomes before and during OA therapy. However, there is scant research on what clinicians should do after risk assessment, especially if they are concerned about the risk of overdose or other adverse outcomes for a specific patient.

The VHA has undertaken a number of new initiatives to address this issue. The VHA recently disseminated guidelines for informed consent for long-term OA therapy and distributed patient educational materials called “Taking Opioids Responsibly for Your Safety and the Safety of Others.” Additionally, the Opiate Safety Initiative provides patient- and prescriber-level data to facility leadership in order to identify prescribers whose quantity of OA prescribing may be above usual practices. Finally, recent efforts have made naloxone, a medication which blocks opioid receptors to prevent mortality when an opioid overdose occurs, available to be prescribed to high risk patients. The limitations of this strategy are described in more detail below, but it is important to note that it is only relevant when someone who is trained to identify an overdose and use naloxone is present during the overdose.

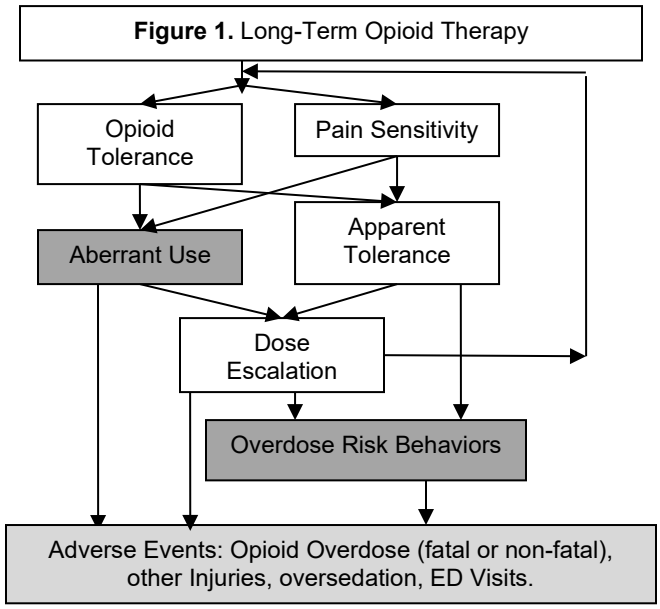
Several VHA initiatives have increased access to behavioral health providers outside of specialty mental health care. The Primary Care-Mental Health Integration (PC-MHI) program co-locates mental health providers within primary care. Additionally, Patient Aligned Care Teams (PACT) seek to deliver comprehensive care, defined as care which “addresses all medical, behavioral, psychosocial, and functional status issues” (Per VHA’s patient-centered medical home concept paper). Consequently, the VHA primary care setting has the personnel to deliver behavioral and psychological interventions due to recent organizational initiatives. However, none of these initiatives have included OA-focused behavioral programs.

Although these recent efforts will likely increase the baseline level of OA safety practices in VHA, the potential efficacy of these stakeholders’ efforts is limited by the lack of evidence based strategies to reduce patients’ risky behavior. Specifically, these efforts have not taken advantage of innovative and state-of-the-art strategies to enact behavior change, which are likely to result in greater changes than educational efforts alone. Additionally, concurrent implementation of approaches that impact prescriber behavior and those that impact patient behavior are likely to be necessary to have a meaningful impact.[4,23] To date, few studies have examined interventions addressing OA overdose-related behavior, and none have used an experimental design or have been conducted within the VHA.

Existing overdose prevention strategies. An evaluation of prescription drug monitoring systems found that states with these programs have not had greater reductions in overdose mortality rates compared to states without these programs.[24] Thus, additional programs that change both patient and provider behaviors related to OA overdose are needed.[23] Existing individual-level overdose prevention delivered to non-clinicians have focused on improving bystander response to witnessed overdoses, primarily through distribution of naloxone,[25-28] based on the premise that opiate users are likely to witness the overdoses of other opiate users.[29] These programs have traditionally been provided through needle exchange services and other drug treatment

services that serve heroin users.[30] The sole exception to this is one program that used this model in primary care to provide naloxone to family members of patients who are prescribed OAs.[31] Extant evidence for these programs is observational. Additionally, although it has been established that overdoses among heroin users are often witnessed,[29] it is unknown how often OA overdoses among pain patients occur in the presence of others. A recent cost-effectiveness analysis predicted that, even if 20% of the heroin users in a community were trained in naloxone distribution, only 6% of heroin overdoses would be prevented.[32] These data suggest the need for complementary approaches aimed at reducing an individual's overdose risk behavior. Although the recent initiative to provide naloxone to VHA patients recommends that providers complement the naloxone training with patient education, this education has not been tested, and may not be sufficient for altering substance use-related behaviors.

Relevant conceptual models. The intervention will be studied as a selective prevention program, in that participants will be on long-term OA therapy and have a risk indicator for overdose (moderate to high dose). Overdose death, a highly significant but relatively rare outcome, would not be an appropriate primary outcome. Instead the primary outcomes will be overdose risk behavior and OA use (aberrant use or pattern of increasing dose), and secondary outcomes are self-reported non-fatal overdoses, other OA-related adverse events, functioning, and safe OA handling.



Our framework is informed by Ballantyne & Mao's model of adverse effects of OAs. Repeated OA use leads to pharmacological tolerance and increased pain sensitivity, both of which contribute to apparent tolerance, and a need, or perceived need, for a dose increase. We add that OA tolerance and pain sensitivity increase the likelihood of aberrant use, which in turn also leads to dose increases, and subsequent adverse outcomes. The development of tolerance and dose increases can lead to overdose risk behaviors (e.g., consuming a high total dose, breaks in use with resumption of normal use). These processes can be cyclical. Additionally, reducing the proportion of patients on potentially unnecessarily high doses of OAs is a goal of the Opioid Safety Initiative. The proposed intervention may provide a complementary approach by decreasing factors that lead to dose escalations and aberrant use.

Prior research has confirmed several of the theorized associations with adverse outcomes described in this model. Higher doses are associated with overdose (fatal and non-fatal and of any intent) as well as ED visits.[12,18,33] A study by the investigators among individuals with substance use disorders found that both pain and aberrant OA use are associated with overdose, but aberrant OA use may mediate the association between pain and overdose.[34] Overdose risk behaviors associated with risk of overdose in individuals with substance use include: combining substances,[35-37] returning to usual level of use after abstinence,[37,38] and injecting.[39] Some aberrant use behaviors have been connected to overdose; for example, obtaining OAs from multiple prescribers is associated with overdose.[40]

The intervention content is based on motivational enhancement, which is guided by behavior change theory[41] and motivational interviewing.[42] Per behavior change theory, increasing self-efficacy and motivation is essential to enacting behavior change across a wide spectrum of health behaviors. The intervention content is also informed by a psychosocial model of pain and substance use.[43] Although initial pain is often biological in cause, the maintenance of pain over time reflects perceptual, affective, behavioral and physical responses. The fear-avoidance model of chronic pain[44] describes the transition from localized injury to chronic pain. A cycle of negative outcomes is observed when a specific painful stimulus causes an individual to assume the worst, referred to as "catastrophizing." This cognitive bias leads to greater fear of re-injury, which increases the avoidance of activities and maladaptive coping strategies, such as aberrant OA use and risky use of other substances. The intervention content will reflect this perspective and include tailoring on beliefs regarding pain and OAs.

Motivational enhancement interventions. Motivational Enhancement (ME)[9,10] is an effective strategy for enacting behavior change.[45] To date, ME approaches have been applied to OA use,[46] with limited data available. To our knowledge, ME methods have not been studied in relation to overdose risk behavior (OA-related or otherwise) beyond the pilot work conducted by the study team (described below). The tone of ME is non-judgmental, empathetic, and encouraging, with a focus on supporting the participant's autonomy. There are three primary phases: Explore, Guide, and Choose.[10, 47, 48] During Explore, the therapist will explore perceptions about OA safety and risk, behavioral history, and goals/values/strengths. During Guide, the therapist uses an Elicit-Provide-Elicit framework, in which the therapist asks open-ended questions, followed by guided summaries and additional open-ended questions, to elicit commitment talk. During Choose, specific cognitive and behavioral skills are imparted and the participant will be prompted to identify goals and strategies to reach those goals. Primary therapist tools are: (1) reflective listening/statements (restating concerns, goals, and problems); (2) rolling with resistance (agreeing with the participant's statements of why change is difficult); (3) eliciting change talk (assessing confidence, interest, and commitment to change); and (4) reviewing tools and planning for reducing risk behavior.[10] A key feature of the proposed intervention will be tailoring, a process by which information about an individual shapes the content. Three tailoring strategies are[49]: (1) overt personalization; (2) feedback about health behaviors, and (3) content matching of messages. Tailoring aims to enhance cognitive pre-conditions for message processing or acceptance (receptivity), and enhance message impact (salience) by selectively modifying behavioral determinants of desired outcomes. Tailoring allows broad topics to be narrowed to participant experience, maximizing impact in a relatively brief session.

Summary of background. OA-related overdoses have increased substantially, and patients receiving OAs for pain in clinical contexts are at increased risk for OA overdose and other adverse outcomes. As a result, OA-related overdoses have come to represent a significant challenge to the VHA's ability to ensure the safety of its patients. Surveys of patients treated with OAs indicate that risky behaviors are highly prevalent. ME brief interventions and cognitive behavioral approaches provide a framework for reducing risky OA use by providing tailored messages that are responsive to the specific behaviors and barriers to change of a particular patient.

Preliminary work. The proposed study will be conducted by a team of experts in health services research, randomized controlled trials, primary care, internal medicine, psychology, and psychiatry. Additionally, the study team has specific expertise in research related to adverse OA-related outcomes, pain management, aberrant drug-related behaviors, motivational enhancement interventions, and cognitive behavioral interventions for pain.

Prior work on adverse safety outcomes. Drs. Bohnert, Ilgen, Bair, and Blow conducted a comprehensive study of OA regimen and unintentional OA overdose among Veterans.[12] This study resulted in the VHA issuing new treatment guidelines for OA prescribing in 2011[17] and led to changes in OA prescribing guidelines generally.[50] Dr. Bohnert's CDA research has also included an examination of temporal trends in VHA OA prescribing and OA overdose (in press). We found that the estimated proportion of VHA patients who receive OAs in a given year increased steadily from 17.4% in fiscal year (FY) 2001 to 24.1% in FY2009. Concurrently, the rate of OA overdoses among VHA patients has increased. Drs. Clay and Silveira have been involved in the implementation of the Opioid Safety Initiative and the long-term OA informed consent process at the Ann Arbor VA.

Dr. Bohnert has conducted research on drug overdoses broadly, including studying trends,[51] environmental factors,[52, 53] and overdose witness behavior.[29,54] Drs. Bohnert, Ilgen, and Blow conducted a study of the association of psychiatric disorders with risk of overdose among VHA patients;[8] all psychiatric disorders were associated with risk of unintentional overdose after adjustment for patient characteristics. Drs. Blow, Pfeiffer, Ilgen and Bohnert have collaborated on studies of suicide among VHA patients, including examinations of: trends over time,[55] suicide as it relates to pain[56,57] and prescription pain medication misuse,[58] psychiatric disorders and risk of suicide,[59, 60] and suicide risk assessments.[61] Additionally, Dr. Ilgen was the Principal Investigator on a study to develop a cognitive behavioral suicide prevention intervention and also an HSR&D study examining suicide risk management practices in VHA substance use disorder clinics.[62] Drs. Bohnert and Ilgen have also examined suicide and unintentional overdoses as related outcomes.[63, 64]

The study team has also examined treatment prior to OA overdose death among VHA patients. In a sample of 985 OA overdose decedents who had a VHA medical visit in the two years prior to their death, 51% had a primary care visit in the 90 days prior to their death and 76% had been seen in primary care in the year

prior to their death. Thus, VHA primary care clinics are a key setting for selective overdose prevention efforts.

Prior work on aberrant opioid use behaviors. Drs. Bohnert and Ilgen have collaborated in several studies of aberrant OA use using items from the Current Opioid Misuse Measure (COMM[65]). The study investigators developed a questionnaire on pain medication expectancies,[66] which included three domains: pain reduction, negative experience reduction, and pleasure/social enhancement. Drs. Bohnert and Pfeiffer recently collaborated on using of select items from the COMM in a clinical capacity with 80 PC-MHI patients at the Ann Arbor VAMC as part of a quality improvement effort. The items were included as part of the intake screening completed by all PC-MHI patients, and the materials indicated that information may be shared with other members of the patient's care team. In total, 24% of patients reported OA use in the past month, and among those with use, 59% reported recent aberrant OA use. These data highlight the willingness of VHA primary care patients to disclose aberrant OA-related behaviors to a PC-MHI provider, underlining the potential for translation of the intervention to "real world" PC-MHI settings.

Randomized controlled trials (RCTS). The study team has extensive experience with conducting RCTs. This has included RCTs related to pain; Drs. Ilgen and Bair have both directed trials of pain management for VHA patients. Dr. Bair is currently the PI of a HSR&D-funded RCT comparing pharmacological and behavioral interventions for the treatment of chronic lower back pain. Dr. Ilgen is the PI of a HSR&D-funded RCT of a cognitive behavioral intervention delivered in addictions treatment to Veterans with comorbid pain and substance use disorders. Study team members have also previously recruited for a RCT of a brief intervention for alcohol use in Ann Arbor VA primary care.[67]

In addition to the two pain-related randomized controlled trials led by study team members, study investigators have collaborated on ME brief intervention trials. Drs. Blow, Ilgen, Walton, Bohnert currently collaborate on two NIH-funded RCTs of ME interventions to address risky substance use (PI: Blow for both). Dr. Walton is the PI of an ongoing RCT of an ME intervention for underage drinkers in the emergency department (ED). Follow-up has exceeded 80% in our RCTs, under the guidance of Dr. Walton.[68-70]

Intervention development. The study team recently completed recruitment for a pilot RCT of a behavioral OA overdose prevention intervention in a non-VHA ED setting (PI: Bohnert, funded by CDC). This was preceded by a developmental pilot project, for which we collected qualitative interviews with 33 patients with past month aberrant OA use and a prior non-fatal overdose. Interview topics included experiences with using OAs and what happened during the respondent's most recent overdose. From this information, we developed and piloted a ME intervention to address OA overdose risk behavior.

For the pilot RCT, Drs. Bohnert, Blow, and Walton refined the intervention by expanding content on pain coping, creating a computerized guide, developing an enhanced usual care (EUC) condition, developing therapist training protocols, initiating weekly supervision, developing a measure of overdose risk behavior (in conjunction with a national team of experts), and adapting measures of precursors of behavioral change (e.g., self-efficacy). In total, 203 participants were randomized. Because follow-up is still on-going, outcomes have not been analyzed. However, Drs. Blow, Bohnert, Ilgen and Walton also recently completed an RCT of ME for risky substance use among ED patients (R01 DA026029; PI: Blow). This study recruited patients from the Hurley Medical Center ED, and achieved 81% to 87% successful re-contact of participants. At 3-months follow-up, among participants age 25-34, those randomized to a computer-based ME intervention had significantly fewer days of aberrant OA use (IRR=0.64, $p<0.05$). This effect was not seen for other age groups.

This ongoing and completed work will not be sufficient to understand the effect of such an intervention for Veterans prescribed OA therapy due to both the scope of the study (pilot RCT) and the differences between patients and settings. However, these experiences will allow us to rapidly modify the existing intervention materials. Thus, this prior work will facilitate the study of an intervention to address overdose risk behavior among Veterans receiving chronic OA therapy, a population for whom this is a highly significant problem.

Summary of prior work. The team brings substantial expertise related to aberrant OA use, overdose risk behavior, and outcomes of OA use. Drs. Bair and Ilgen bring research and clinical experience related to pharmacological and behavioral pain treatments. As the Director of the Ann Arbor PC-MHI clinic, Dr. Pfeiffer brings additional expertise in the integration of ME in primary care clinics, which will aid in future implementation. Additionally, the study investigators have demonstrated experience conducting RCTs and retaining high levels of participation over follow-up. The team also has expertise in suicide risk management that will be relevant to safety protocols and intervention content. Finally, the study team has developed and piloted a promising brief intervention to reduce OA-related overdose risk. Thus, the research team has both the necessary expertise and content area knowledge to successfully conduct the proposed study.

SIGNIFICANCE

Reducing the number of overdoses, particularly those that may be an iatrogenic result of OA therapy, is imperative to VHA's mission to provide safe care to the nation's Veterans. Although new VHA initiatives to address prescribing practices and provide basic patient education are important first steps, concurrent strategies that increase patients' motivation to engage in safe OA use are critical to reversing the alarming increases in OA overdoses. The proposed study is highly significant because of the recent increases in medical use of, and overdoses related to, OAs in and outside of VHA. It will be the first study to examine a brief intervention to reduce overdose risk behavior among VHA patients on long-term OA therapy, with full integration in PC-MHI. Thus, although the scope of this study will not allow determination of whether the intervention would be effective at all VHA treatment locations, the intervention will be able to be delivered at all VAMCs because of the national requirement to provide PC-MHI services. This will facilitate future integration into clinical care as well as implementation studies designed to be nationally representative. Furthermore, the intervention was designed to complement and/or enhance the impact of recent VHA initiatives, such as OA informed consent and naloxone training and prescribing to caregivers.

Relevance to VA health care. Approximately half of VHA patients experience pain on a regular basis.[71] Among OEF/OIF/OND Veterans, pain is among the most common symptoms reported.[72] OA therapy constitutes a primary modality of chronic pain treatment and is the focus of many treatment guidelines.[1,22] In a study of VISN20 patients with persistent pain in 2008, 72% were prescribed an OA at least once in the year.[3] Pain in Veterans is generally associated with poor functioning and more psychiatric problems.[71,73,74] Methods to maintain historical gains in pain care access while reducing the potential harms are essential to the quality of life of VHA patients.

Prior research by study team members has demonstrated that VHA patients are at an elevated risk of unintentional overdose compared to the general U.S. population.[6] Analysis conducted by the study team found that there were 12,233 overdose deaths among VHA patients between 2001 and 2009. Reliable estimates of the number of non-fatal overdoses are difficult to determine from VHA medical records alone, but CDC data indicate that there were 22.9 non-fatal overdoses treated in EDs for every fatal overdose in the U.S. during this time period.[75] Consequently, there were an estimated 280,136 non-fatal overdoses serious enough to merit ED treatment among VHA patients between 2001 and 2009.

The VA Uniform Mental Health Services Handbook requires that "primary care, medical specialty, and mental health services … use case-finding methods to identify patients who … misuse prescription or over the counter agents." The proposed study will further this goal by providing data on an intervention that can be implemented with patients who have pain and are engaged in aberrant use of OAs. Ultimately, the proposed project could lead to reductions in overdose mortality among VHA patients.

Responsiveness to HSR&D priority areas. This proposal is responsive to the HSR&D priority for Investigator-Initiated Research focused on mental and behavioral health (Priority E). It will primarily focus on issues of behavioral health, namely OA use and other substance use, while also attending to issues of mental health. This application addresses the stated interest of HSR&D to "enhance the continuum of care for substance use disorders" by fostering the expansion of primary care treatments related to substance use, which to date is lacking for OAs. This proposal will also serve VHA patients receiving long-term care (Priority D) for chronic pain. Additionally, it is responsive to HSR&D's interest in post-deployment health by examining OEF/OIF/OND status as a moderator.

Contributions of the proposed work. The proposed study will increase our understanding of strategies to reduce adverse outcomes related to long-term OA use among VHA patients with pain, which is a significant problem in VHA, given the scope of OA use in VHA. If successful, PC-MHI clinics will have a novel intervention to prevent adverse OA-related outcomes. Additionally, the ME model has not previously been applied to OA overdose prevention, with the exception of the team's pilot study. The examination of mediators of intervention effectiveness can inform the refinement of theoretical models of brief interventions and behavior change.

VHA is a national leader in integrating behavioral health clinicians into primary care. As part of the Evidence-Based Therapy Roll-Out, VHA has provided training in ME methods through a two-day intensive training course. The focus of the training is an ME intervention to increase motivation to attend specialty addictions treatment. This effort demonstrates the potential for sustainable translation and implementation of

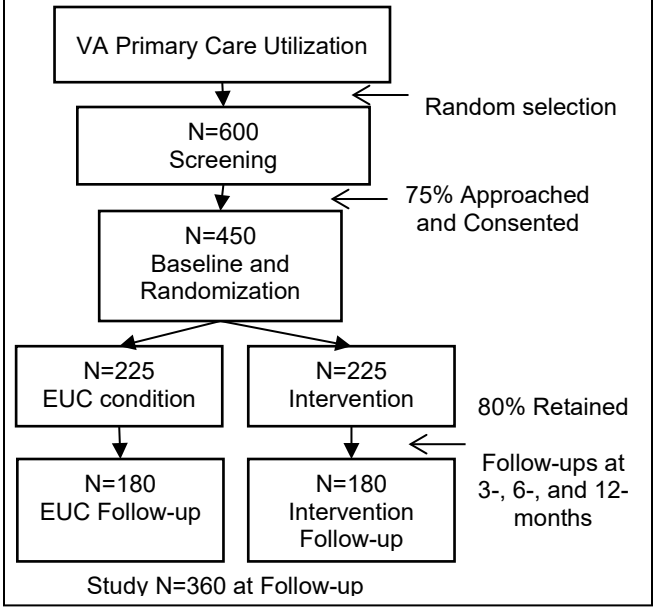
the proposed intervention. Specifically, current VHA primary care clinicians, particularly PC-MHI clinicians, who have received training in ME through this initiative would be able to tailor delivery of the proposed intervention.

RESEARCH DESIGN AND METHODS

Overview of study design and approach. The POST study will refine an OA overdose prevention intervention and conduct of pragmatic randomized controlled trial of the intervention in the VHA PC-MHI setting. We will modify intervention materials, train staff, conduct focus groups with primary care-based opioid prescribers, form a patient advisory panel, and pilot the intervention. Next, we will conduct an RCT of the intervention compared to an equal attention, enhanced usual care (EUC) condition, building on the current OA informed consent process, with 450 Veterans receiving long-term OA therapy at dose levels of 20 morphine-equivalent mg (MEM)/day or more. Participants will be re-assessed over one year post-intervention to assess for immediate psychological effects as well as short- and long-term sustainability of effects on outcomes.

Based on our prior work,[12] we estimate that approximately 88% of patients receiving an OA for a pain condition will not have a cancer diagnosis (and thus will not be excluded on the basis of having terminal cancer) and ~45% of patients will be receiving 20 MEM/day or more. In fiscal year 2012, 6,553 patients were treated in Ann Arbor primary care clinics and prescribed OAs. We estimate that 1,537 patients will screen positive to be approached for recruitment based on medical records. We will randomly select 600 individuals to approach. We estimate that 75% of individuals who are randomly selected to be approached will not be missed, will not meet any exclusion criteria, and will consent to participate, resulting in a baseline sample size of *450*. We also estimate that 80% of participants will be reached for the 12-month follow-up assessment.

Figure 2. Study Diagram



Setting. Recruitment will be carried out at primary care clinics at the VAMC in Ann Arbor. Per Opioid Report data, 41,106 patients were treated at the Ann Arbor VAMC in the first quarter of fiscal year 2014; 26.7% were prescribed an OA in that quarter and 5.9% of Ann Arbor VAMC patients who received an OA experienced a serious adverse effect in that quarter, compared to 6.1% nationally. We estimate that the 5.5% of patients treated with an OA in primary care at Ann Arbor are female, 1.5% are of Hispanic ethnicity, 9.8% are African American, 88.5% are Caucasian, 0.8% are American Indian, 0.5% Asian, and 0.4% are Native Hawaiian or Other Pacific Islander.

The study therapists will be integrated into the VA PC-MHI clinic. This integration will mean that the study therapists will be located in PC-MHI, attend PC-MHI staff meetings, and receive additional clinical and administrative supervision from the PC-MHI director (co-I Dr. Pfeiffer). Staff at the Ann Arbor PC-MHI clinic are primarily Master's-level social workers. Although PC-MHI largely treats patients referred from primary care clinics, the PC-MHI clinic is co-located, and will recruit directly from primary care for this study.

Patient sample.

Inclusion criteria. Eligible participants will be those who are prescribed 20 MEM/day or more as part of long-term OA therapy and who receive treatment at primary care clinics at the Ann Arbor VAMC. Long-term OA therapy will be defined as at least 84 days covered within the past 90 days. The Principal Investigator will use discretion when it is clear that the eligible participant is on long-term OA therapy, despite not having a prescription written exactly for at least 90 days (e.g. small breaks in therapy, or prescriptions intended to be taken consistently but at a lower frequency than written resulting in gaps between fills). When necessary, the Principal Investigator will confer with the physician co-investigators who are experts in chronic pain management (Drs. Clay, Silveira, Bair). The criteria of prescribed OA dose of 20 MEM/day or greater was selected because patients prescribed this dose are at increased risk of overdose death.[12]

Exclusion criteria. To increase generalizability of findings, a minimal number of exclusion criteria will

be used. These are: 1) plans to stop OAs or reduce dose to below 20 MEM/day in the next 6 months, 2) use of fentanyl, due to the difficulty in determining morphine equivalency (preliminary work indicated that less than 2% of VHA patients receiving OAs are prescribed fentanyl), 3) only opioid type used is Tramadol/Ultram because it is not subject to the long-term OA therapy informed consent process 4) prescribed or using Suboxone 5) terminal cancer, 6) acute risk for self-harm related to opioid use requiring immediate treatment (see next section), which is then likely to result in a reduction or cessation in opioid therapy, 7) moderately severe cognitive impairment (based on a validated six-item cognitive screener[76]) to ensure accuracy of data, 8) pregnant women, and 9) inability to give informed consent. Participants may be included or excluded at the discretion of the Principal Investigator based on participant or study staff best interest (e.g. if participant should become physically or verbally aggressive towards study staff, or if study staff know a patient or their family personally, in order to fully ensure participant privacy).

Patient safety. During the study, we may determine that a participant is at serious, imminent risk for serious self-harm related to their OA use. Study staff will notify the participant's prescriber in this situation and will make additional referrals to mental health or emergency services as needed. These participants will be withdrawn from the study and will not be included in analysis (see section on Feedback to Providers on page 11). For non-OA related risks, such as suicidal ideation, staff will discuss the risks of participation with the patient and review screening responses and the medical chart (e.g., for ongoing mental health care) to decide study eligibility. If any of these determinations are unclear, staff will consult with the supervising psychologist (Dr. Ilgen) or psychiatrist (Dr. Pfeiffer), both of whom have expertise in assessing suicide risk. Participants who report acute suicidality will be able to continue with study procedures at a later time and will be referred to same-day care through either a PC-MHI-based Psychiatrist or the ED. If treatment needs are not urgent, the participant will be referred to specialty mental health and continue with study protocols. Those participants in the trial who report suicidality at a 3-, 6-, or 12-month follow-up assessment will be connected to the appropriate services (outlined in the Safety Monitoring Plan section on page 21).

Usual care, intervention, and EUC procedures. Both intervention and EUC participants will receive the Long-Term OA informed consent and will review the VHA's "Taking Opioids Responsibly for Your Safety and the Safety of Others" pamphlet with a study therapist (usual care). The study therapists will coordinate with the patients' prescribing physicians to document this process if a participant had not already provided informed consent. For the intervention condition, the informed consent process will lead to a tailored, ME-adherent discussion of reducing the risks of OAs, but for the EUC condition, the informed consent process will be followed by psychoeducation on topics related to pain management, will not be tailored, will not include elements of ME, and will not include content on overdose risk behaviors. If a patient expresses a wish to change their OA regimen after any of the intervention or control content, the study therapist will assist the patient in arranging an appointment with their prescriber.

Intervention. The intervention session is tailored on knowledge, values, concerns, barriers, and skills/tools for managing pain. It combines elements of ME and cognitive behavioral therapy (CBT) and uses the structure of ME brief interventions. Participants are presented with a variety of risk reduction strategies, including abstinence of all substances except prescribed medications, not combining substances, and taking medications as prescribed. Participants are provided with a number of strategies for coping with pain that may reduce reliance on OAs, such as meditation, activity pacing, stretching, exercise, ice or heat, eliciting support from friends and family, and distraction. The therapist prompts the patient to reflect on which tools are likely to help him/her personally, barriers to using those tools, and plans for overcoming those barriers. The intervention does not recommend that participants stop or reduce their OA use below prescribed levels, but participants who express concern that the benefits of OAs may be outweighed by the harms are guided on how to discuss this concern with their prescriber. The session includes the following organization:

Explore: 1.) Introduce purpose of the session, affirm autonomy to make decisions; 2.) Elicit participants' strengths, values, and goals. 3.) Guide discussion of tailored behavioral history (OA use, other drug and alcohol use, overdose risk behaviors) and pain experiences using open-ended questions/probes.

Guide: 1.) Review role of cognitive factors in pain; 2.) Review risk factors for overdose, with particular emphasis on risk factors for OA overdoses, using an "elicit-provide-elicit" approach;[10] 3.) Review other risks of OA use (oversedation and resulting injuries, impaired driving) and safe storage and disposal; 4.) Guide discussion of potential changes to risk behaviors and use of tools, using menus/lists, eliciting benefits of change, reflective statements, clarifying ambivalence, and anticipating and discussing barriers to change; 5.) Use confidence rulers to elicit importance, confidence, and intention to change.

Choose: 1.) Elicit goals for risk behavior. 2.) Discuss strategies for storing OAs and talking to your doctor if you are taking more or less than s/he has prescribed using an "elicit-provide-elicit" approach. 3.) Review tools/options of overdose risk reduction strategies and tools for making behavioral changes. 4.) Review coping strategies for managing pain and plans to overcome barriers. 5.) Summary.

Note that the primary focus of the intervention is on prevention of overdoses that occur without overt suicidal intent, the latter of which make up only a small proportion of overdose deaths.[77] Our prior research indicates that similar psychological risk factors exist for overdoses ruled unintentional and intentional,[63,77] and psychological factors like hopelessness and impulsivity may precipitate overdoses across the spectrum of intent. For participants who identify mental health issues as relevant to their overdose risk, the therapist will explore strategies for identifying and addressing mental health symptoms when they occur.

During the start-up phase of the project, the team will adapt the intervention manual for VA primary care. It will then be shared with a group of primary case-based opioid prescribers and a Patient Advisory Committee at the study site. The intervention will also be piloted with a small number of patients who agree to participate (expected to be 10, but will vary based on need). These steps will provide key feedback on clinical utility and feasibility, leading to further refinement.

Enhanced Usual Care (EUC) condition. In addition to covering the VHA's long-term OA informed consent process, the control therapist will provide participants educational content with an overview of pain conditions. The overall style will be didactic. This EUC condition will include some information related to risks of OA use as part of the informed consent and will consequently have sufficient face validity as an intervention on OA safety to effectively blind participant to randomization. The VHA pamphlet that is part of usual care lists alternatives to opioid therapy, such as exercise, weight loss, relaxation training, and injections, some of which are also strategies for pain coping. However, the EUC therapist will not use the ME approach of discussing which of these treatments the participant might consider using and strategies for overcoming barriers to their use. Thus, the control condition represents the delivery of standard aspects of VHA care related to OA safety under usual practices and also accounts for potential effects of attention. Therefore, this study will determine if the intervention leads to greater reductions in overdose risk behavior as a result of ME therapeutic style and specific content, rather than due to amount of contact with a clinician.

Feedback to prescribers. We will notify all participants' prescribers that their patient is at risk for overdose due to their medication regimen and/or OA use behaviors. The notification will include information that we will have discussed this risk with the patient and will occur at the point that intervention or EUC protocols for that patient are completed. This notification will be done for both intervention and control participants to avoid potential differential effects on measurement (because notification to providers could impact future self-report).

We will implement an additional notification process to the prescriber if the patient is at acute risk for self-harm. Focus groups with primary care-based OA prescribers at the study site (n=20) allowed us to understand what situations would merit a notification, how providers want to be notified and how they will use that information. The situations include, but are not limited to, using their opioid prescription along with heroin, cocaine, benzodiazepines, non-VA opioid prescription, or snorting or injecting their medication if it is not written as such. This list may change if the study team notices trends in participants that are increasing their risk of overdose and death. Any changes will be discussed and approved by the principal investigator and the clinical co-investigators (Drs. Bair, Clay, Silveria). Providers will be notified by study staff in-person with the participant when possible, or messaged in CPRS or Lync/Skype. When messaged, a generic message will be sent to protect the participant's privacy. Study staff will only mention the facts and not make any clinical conclusions or suggestions (e.g., only state that the participant endorsed using heroin, or tested positive for cocaine). We have developed and presented a notification plan at PACT staff meetings prior to the start of enrollment to solicit feedback and refine the plan. We anticipate that the situations that will be defined as serious, imminent risk will occur relatively infrequently.

Training protocol and assessment of fidelity. Drs. Bohnert, Ilgen, Blow, Pfeiffer and Walton will conduct a two-day training involving a review of ME and CBT principles and techniques, the rationale for the intervention, a detailed description of the intervention, and role playing. Dr. Bair will provide training so that the therapists will be well versed in OA therapy and the evidence base for pain treatment. The study coordinator will participate in the intervention training to enhance his/her ability to monitor fidelity and contamination. The therapist hired to provide the EUC condition will have a parallel training process to learn EUC protocols. All

staff will receive training on handling crisis situations and adverse events. The intervention therapist will receive ongoing training biweekly from Dr. Ilgen. With participant permission (>90% in prior work), all sessions will be audiotaped. Sessions completed over the phone will follow the same audio recording script and protocol as in-person sessions. A 20% random sample will be reviewed by the coordinator and an investigator to prevent and monitor contamination in the EUC condition and measure fidelity and therapist competence in the intervention condition. Likert items to rate fidelity to the intervention and therapist competence will be developed based on the Yale Adherence and Competence Scale (YACS) and cover topics such as adherence to ME principles, general supportiveness, coverage of content, and non-therapeutic behaviors.[78] These ratings will be generated on an ongoing basis to inform supervision.

Randomized trial.

Recruitment and screening procedures. Study staff will conduct initial screening of participants (after obtaining a HIPAA waiver of informed consent for recruitment screening purposes) via logs of the patients scheduled for appointments and extracted medical records. Screening will include diagnoses, OA use (dose and length of treatment), social security numbers, and OEF/OIF/OND veteran status. The patient's social security number will be used to identify the eligible participant in the electronic medical record, which will be necessary particularly with common names. For more information on the medical chart extraction, please see the Measures section on Medical Chart and Administration Data Extraction on page 15. The data analyst will use standard ratios[11] and established calculation methods[12] to determine morphine-equivalency for OAs. When possible, research staff will then create a list of potentially eligible patients with appointments on a weekly basis. This report is available to all primary care staff, and includes patients on narcotics and their upcoming primary care appointment.

Additionally, study flyers will be posted around the primary care clinic, physical therapy clinic, and other related clinics in the Ann Arbor VA. The flyers will mention our study and provide our study contact number for participants to find out more information. Similar to our current protocols, we will confirm a patient's eligibility through review of pharmacy, Opioid Therapy Risk Report, and chart review. The Primary Care-Mental Health Integration (PC-MHI) staff and providers will be given the same flyers that they may distribute to appropriate patients. They will not be involved in the recruitment of participants, other than handing out flyers. While this will expand our recruitment efforts, we will emphasize that the PC-MHI staff will only provide the patients with the flyer. The flyer will introduce the study and provide contact information. Study staff will confirm that any interested patient's involvement in the study will not affect their primary care or VA treatment. Their involvement is completely voluntary.

The study analyst will randomly sample from the potentially eligible participants. OEF/OIF/OND Veterans will be oversampled to have sufficient numbers to examine this as a moderator. Those with OA doses of 100 MEM/day or more will also be oversampled. In our prior study of VHA patients treated with OAs, 33.6% had a psychiatric diagnosis; thus, we do not anticipate that oversampling will be required to have sufficient variability in baseline mental health to examine this factor as a moderator. We may send a letter to patients selected to be approached in advance of their appointment, which will briefly describe the study and provide a number to call to "opt out" of being approached. This method has been approved for prior work at the study site and was adopted based on recommendation from our clinical partners to allow patients sufficient time at the Ann Arbor VAMC to complete study procedures. The day before the scheduled appointment, research staff may call the patient to provide more information about the study and their participation, and to develop rapport with the patient in order to more easily identify the patient at their appointment. This conversation will also serve as a reminder to the patient to allow more time if they choose to participate in the study.

Staff will approach selected patients in the waiting area or after their appointment ends and will describe the study briefly. Additionally, the patients' documents for the visit will indicate their eligibility so that their provider can remind them that they may be approached about participating in a research study, consistent with IRB-approved processes in ongoing studies at the study site. Staff will escort interested participants to an area where privacy and confidentiality can be maintained to conduct informed consent for the study and additional screening procedures. Privacy during assessments will be achieved by making sure no one can overhear the conversation. If applicable, research staff will ask others to leave the room during interviews. Participants who are not able to stay after their medical appointment will be asked to schedule an appointment with study staff to complete enrollment. Additional screening questions will determine: 1) whether the potential participant has stopped using OAs, 2) whether the potential participant will reduce their OA dose to ≤ 20 MEM/day in the next

6 months, 3) cognitive impairment, and 4) any other exclusion criteria not noted from the medical record. Participants will be given the option to complete their baseline assessment and receive the intervention or EUC protocols at that time, or will complete it within 5-10 days (in-person or over the phone). Participants with limited time will be given the option to complete the informed consent process in-person, then follow-up with a phone call to complete the survey assessment and intervention. This will be used as a last resort for those participants who have restricted availability or concerns with travel. Participants who chose this option will be able to complete the urine drug screen in-person after completing the informed consent document. They will be provided with the handouts for the session at the time of the in-person informed consent process. Minimal de-identified data (e.g., gender, race, age, reason for refusal) will be collected on eligible patients who are not recruited or refuse to participate in the study to better understand how they differ from those that do participate on key factors and reasons for refusing participation so the study can understand potential bias in sample frame.

Randomization. Participants will be individually randomized to receive either the intervention or EUC after completing the baseline. The coordinator will supervise the randomization, which will be conducted by the analyst, using computerized block-randomization stratified by OEF/OIF/OND status in blocks of 10.

Intervention and EUC condition delivery procedures. The intervention and EUC procedures will each take approximately 30 minutes to complete, in addition to the chronic OA therapy informed consent. These sessions will take place in a private room or over the phone in a private office to ensure privacy and confidentiality. Consistent with our prior interventions, the sessions will be computer-aided to enhance fidelity. For the intervention, the therapist uses the computer aid to progress through a series of prompts, which ensures that each step of the intervention is covered and reminds therapists of specific ME tools relevant to each step. The computer aid also includes screens with suggested options/choices that can be shared with participants who have trouble generating goals, values, strengths, and tools without prompting. The EUC condition will also use a computer aid that will include a series of prompts and non-interactive visual aids related to the content of that condition. Feedback to the participants' prescribers will be given based on the protocol developed through the process described above.

Risk of contamination. There are three possibilities of contamination: (1) Contamination of the intervention with EUC. The EUC will present general educational information on pain. The potential discussion of this information by EUC participants with intervention participants should not "contaminate" the intervention condition with any information that would not normally be available. (2) Contamination of EUC with elements of the intervention. If any contamination does occur, it is expected to be minimal. Contamination of EUC with elements of the intervention will be closely monitored. Intervention therapists conducting the EUC session will be trained on strict adherence to the manual. The EUC sessions conducted by the intervention therapist will be reviewed for adherence and contamination to instruct and change before the next session. However, we will assess for changes in self-efficacy, motivation, knowledge of risk factors in all participants and will conduct ongoing fidelity assessments of EUC sessions. (3) Contamination of standard treatment. Both conditions will be provided by research staff who will not directly influence the course of treatment at Ann Arbor VAMC during the study.

Patient Advisory Committee. We will form a committee of patients from the study site. We will seek to have male and female Veterans, OIF/OEF/OND Veterans and Veterans of less recent conflicts, and Veterans with and without comorbid mental health problems on the committee. This group will be asked for advice to refine the study protocols, will meet twice yearly during active recruitment to be updated on progress and provide feedback, and will meet after data collection to provide advice for implementation.

Data collection procedures. Assessments will be self-administered paper-pencil surveys, and research staff will be available to clarify questions. There are five assessments: baseline, post-test, and 3-, 6-, and 12-month follow-up. This assessment schedule will be able to measure if intervention impacts both proximal (e.g., self-efficacy) and distal (e.g., overdose risk behavior) outcomes and to allow enough time to pass to detect less common outcomes (e.g., non-fatal overdose and emergency department visits). All assessments will occur in an area where privacy and confidentiality can be maintained and will take up to 1 hour. When the participant has limited time, the assessment may be completed over the phone. For the post-test, the study therapist will have someone else on the team complete that assessment, or schedule a time for another study member to call back the participant. This will ensure that we are collecting accurate feedback from the participants on the

intervention sessions. This length is comparable to prior research assessments at the Ann Arbor VAMC. Privacy during assessments will be achieved by making sure no one can overhear the conversation. If applicable, research staff will ask others to leave the room during interviews. Baseline assessment will occur at the time of recruitment or shortly after. After intervention or EUC procedures, participants will complete a brief post-test assessment to measure changes in knowledge, self-efficacy, and motivation. Participants will be given $30 (+$5 for the urine drug screen [UDS]) for completing the baseline and post-test assessments. Participants will be given an additional $10 at each assessment to assist with travel expenses.

The 3-, 6-, and 12-month assessments will occur in at the Ann Arbor VAMC. In cases where this is not feasible for the participant, the research staff will arrange to meet the participant at a convenient location in the community (e.g. participant home, library), conduct the assessment by phone, or mail the assessment to participants to complete and return to the research team. In cases where the follow-up assessments are conducted via U.S. mail and a participant endorses risk (suicide or opioid, according to our protocol), research staff will make at least three attempts to reach the participant within 72 hours of receiving the survey to further assess level of risk and/or answer questions. Every mailed survey packet may include the resource brochure which includes national suicide hotlines, VA Crisis Line and mental health services. Privacy during assessments will be achieved by making sure no one can overhear the conversation. If applicable, research staff will ask the research subject to have others leave the room during interviews. The research assistant conducting follow-up will be blind to group status. Based on our prior research,[68,69,79] we conservatively estimate that 80% of participants will be interviewed at follow-up. Techniques to ensure high retention include: gathering extensive tracking information, using reminder letters as well as contacting participants by phone, and scheduling follow-up interviews at the participants' convenience. Participants will be contacted two weeks prior to the assessment due date to schedule an appointment. Study staff will monitor primary care appointment logs for participants who have not responded to letter and phone contact and non-obtrusively approach patients in waiting areas. The 3-, 6-, and 12-month follow-up assessments will take approximately one hour to complete and participants will be given $30 (+$5 for a voluntary UDS) for each plus an additional $10 to assist with travel expenses.

Measures. Data will be collected through a combination of self-report, medical records abstraction, and UDS. In general, the baseline survey will assess past year or lifetime while the follow-up assessments will assess the period since the last assessment. For self-report data, questionnaires with established reliability and validity will be used whenever possible. Reviews suggest that self-report drug use data has a moderate to strong degree of reliability and validity.[80] The accuracy of self-reported information on substance use is enhanced when confidentiality is ensured and the interview is administered when the respondent is not intoxicated.[81] The voluntary UDS will be used to improve the validity of self-reported substance use.

Measure title	Baseline	Post-Intervention	Follow-ups
Current Opiate Misuse Measure (COMM)	X		X
Overdose Risk Behaviors (ORB)	X		X
Overdose Experiences, Self –Alcohol (OESWA)	X		X
Overdose Experiences, Self and Witnessed – Drugs (OESWD)	X		X
Treatment Service Review (TSR)	X		X
Alternative Therapies (AT)	X		X
Revised Injury Behavior Checklist (RIBC)	X		X
Pain Treatment Satisfaction Scale (PTSS)	X		X
Safe Storage and Disposal of OAs	X		X
Veterans RAND 12-Item Health Survey (VR-12)	X		X
Knowledge of Overdose Risk Factors (OK)	X	X	X
Overdose Education and Naloxone Distribution (OEND)	X		X

Behavioral Intentions (BI)	X	X	X
Self-Efficacy-Overdose Self (SEOS)	X	X	X
Perceived Satisfaction and Utility (PSU – I & PSU – C)		X	
National Comorbidity Survey (NCS)	X		X
Brief Pain Inventory – Short Form (BPI)	X		X
Pain, Enjoyment and General Activity Scale (PEG)	X		X
Centrality of Pain Scale (CPS)	X		X
Addiction Severity Index (ASI)	X		X
Alcohol, Smoking and Substance Involvement Treatment (ASSIST)	X		X
Demographic information	X	X	X
Military service information (MSI) *not individually labeled but included in Demographics*	X		X

Outcomes. *(Measured at Baseline and Follow-up, except where noted)*

OAs Prescribed. We will determine prescribed OA regimen from pharmacy data using established methods[12] with standard morphine equivalency ratios.[11] The Medication Possession Ratio (MPR)[82] will also be used to measure actual medication use/adherence by accounting for early and late refills. The MPR can identify patients who consistently refill early, an indication of overuse. OA therapy outside of VHA will be assessed and those participants who report being prescribed OAs by non-VHA care providers will be asked about formulation, dose, and prescribed schedule, and the dose and MPR will be adjusted accordingly. Pharmacy data will also be used to determine prescribed dose for the eligibility criteria of 20 MEM/day.

Aberrant OA Use. The Current Opiate Misuse Measure (COMM) is a 8-item self-report of recent aberrant use developed for, and validated in, patients receiving OAs.[65] Items include: getting medications from someone other than the prescribing physician, taking medications differently than prescribed, and taking for reasons other than pain. Patients report their past-month behavior on a five-point Likert scale ($\alpha = 0.86$).

Overdose Risk Behaviors. We have adapted items on overdose risk (ORB) from Strang and colleagues[26] by adding risk factors specific to OAs.[12,18,33,83] This measure was developed with a national consortium of experts. Items include: high dose (more than 100 MEM/day); combining OAs with other substances; route of use; using alone; and returning to usual dose after a period of abstinence. In our pilot RCT, this measure was able to detect substantial between-subject variation, with participants reporting between 0 and 10 behaviors, 70% reporting at least one risk behavior, and a mean number of behaviors of 1.9 (S.D.=2.0).

Secondary Outcomes.

Non-Fatal Overdose Experiences: Established items will be used to assess non-fatal overdose (OESWA and OESWD).[84] For each overdose, we will assess the date, substances involved, intent (categories including “suicide attempt,” “did not want to die but did not care about the risks,” “accident, effect of drug was not expected,” and “unsure”), preceding events, and actions taken by others.

Treatment Use (including ED): Use of specific types of clinical services will be assessed with questions adapted from the Treatment Service Review (TSR).[85] For ED use, participants will be asked “how many times did you visit an emergency room?” and asked what were the problems for which they were seeking treatment and the date of each visit. Parralel questions will assess non-VHA use of addictions, pain, and mental health services. We will assess alternative pain treatment (AT) modalities utilized during baseline and a more extensive list of pain treatments and self-management strategies during follow-up assessments.

Injuries: The Revised Injury Behavior Checklist (RIBC) for adults[86] will be used to identify 4 types of injuries, including those not resulting in use of ED services (overdose will be excluded from this measure).

Over-sedation: Pain Treatment Satisfaction Scale (PTSS)[87] is a 12-item tool designed to assess the OA-related side effects on a scale of 0 (“Did not experience” to 5 (“Extremely bothered”). Over-sedation will be measured as “Excessive fatigue”, “inability to concentrate”, and/or “drowsiness.”

Safe Storage and Disposal of OAs: We will adapt items by McCauley and colleagues[88] designed to assess knowledge of safe storage and disposal of OAs. This measure is sensitive to the effects of a web-based psychoeducation on safe OA storage and disposal.

Functioning: We will use the first item from the Veterans RAND 12-item Healthy Survey (VR-12)[89]. In the interest of reducing patient burden, we will use the single item. This is consistent with health status items

used in many national health studies[90, 91].

Medical Chart and Administrative Data Extraction. Data will be extracted from the CDW Production Domains, and CDW MCA (formerly DSS) NDE, MedSAS Files including VetsNet Files and CAPRI/VistAWeb datesets as well as the Opioid Therapy Risk Report (OTRR). The OTRR allows VA providers to efficiently monitor clinical data related to opioid pain treatment within the electronic medical record (EMR). The OTRR provides a list of patients on long-term opioid therapy with upcoming primary care appointments, along with related opioid risk factors.Opioid pain medications will be requested from CDW MCA NDE pharmacy data. Dates of fills, day supply, prescribing physician, total quantity and dosing and schedule instructions will also be used. We will collect basic demographic information (name, birthdate/age, race, social security number), OEF/OIF/OND service, diagnosis (e.g., terminal cancer), clinic appointment information (date of appointment, type of appointment, etc.), and basic contact information (address, phone numbers) for those receiving long-term OA therapy treatment. These data will be extracted from the staff, patient, appointment, inpatient, outpatient and pharmacy CDW Production Domains, MedSAS Files and/or the OTRR. CAPRI/VistAWeb will be used to check for external appointments. Research staff will confirm upcoming appointment and eligibility Access to real SSN data is needed in order to link the administrative data from the MedSAS datasets, CDW and OTRR to data from chart reviews. In addition to OA regimen, data will be extracted over follow-up to assess VHA service use, diagnoses, mental health assessments, other medication use, and mortality (from the Beneficiary Identification Records Locator Subsystem of Vital Status; mortality will also be measured by information that comes from the contacts nominated by that participant or records databases and obiturary listings). VHA service use, diagnoses, mental health assessments, and other medication use will be extracted from CDW Production Domains, MedSAS files and CAPRI/VistAWeb. We will also examine the chart for information related to the prescriber notification in order to better understand the impact of the notification process.We will use both VINCI and our local VA server for the administrative data extraction of potential patients that fit our eligibility criteria. The use of both storage options will increase our ability to find potential patients in a timely manner and avoid delays due to occasional problems with the transfer of data from VINCI to our local VA server. The OTRR will be saved to our local VA server.

Mediators and process measures. *(Baseline, Post-Test and Follow-up, except where noted)*

Knowledge of Overdose Risk Factors. Knowledge of overdose risk factors (OK) will be assessed with a checklist adapted from prior studies[26] with additional items for OA overdose specifically (OEND). In our pilot RCT, 56% of participants misidentified at least one risk factor. In addition, at Baseline and Follow-up, we will assess participant's involvement in overdose education and naloxone distribution.

Motivation and Self-Efficacy. Behavioral intentions (motivation; BI), self-efficacy, and readiness (SEOS) to change will be measured with 6 visual analog rulers.[92] These constructs are considered critical to ME interventions.[10]

Perceived Satisfaction and Utility *(Post-test only)*. A five-point Likert scale (from "really didn't like it" to "liked it a lot") will elicit satisfaction (PSU-I & C).[93] We will use similarly-structured questions[94] to measure the perceived helpfulness of specific intervention components.

Other factors. *(Baseline and Follow-up, except where noted; collected to inform later implementation, to characterize study sample, and/or to examine moderators of effect)*

Suicidality. We will use select modified items (3) from the National Comorbidity Survey (NCS[95]) that will assess past 12 month suicidal ideation and suicide attempts. Follow-up assessments will inquire about the time since last assessment.

Driving after consuming OAs. For our prior work, we adapted items from the National Survey of Drinking and Driving Attitudes and Behaviors[96] to OA use (included in ORB). Frequency is assessed with a 5 point Likert scale.

Pain Severity and Functioning. We will use select items (7) from the Brief Pain Inventory-Short Form (BPI)[97] to assess pain interference on a 11-point numeric rating scale (0=Does not interfere, 10=Completely interferes). The Pain, Enjoyment and General Activity scale (PEG)[98] is a 3-item questionnaire designed to measure chronic pain in a primary care setting. The Centrality of Pain Scale (CPS)[99] is a 10-item scale used to assess how patients perceive the role of chronic pain in their lives. The CPS has high internal consistency (Cronbach's alpha = .902).

Alcohol and Drug Use Severity. The Addiction Severity Index (ASI)[100] will be modified to allow participants to self-administer the questionnaire. We will use select items (7) from the ASSIST (WHO[101]) to assess alcohol use and problems.

Demographics Information on participants' race, gender, sexual orientation, OEF/OIF/OND status (MSI), marital status, employment status, income, and education will be collected. Contact information and housing status, address, phone number, e-mail (if applicable) and type of living arrangement will also be collected.

Analysis plan. The project's data management and analysis will be supervised by Dr. Bohnert, who received advanced biostatistics training during her Ph.D. in public health. Tests for linearity, independence, missingness, and distributional assumptions will be conducted on key variables. Distributions will guide modeling decisions and normalizing transformations will be used when appropriate.

Although we expect that randomization will balance the groups, we will validate randomization by comparing groups on key variables potentially related to outcomes. If we identify significant group differences, we will adjust for these variables in models. The EUC condition will be designed to be equal-attention, but we will examine potential associations of the outcomes with length of session in sensitivity models.

Mixed effects regression models (described below) will allow the use of data from all participants, including those with incomplete follow-up, and provides unbiased parameter estimates under the missing-at-random assumption.[102] If the missing-at-random assumption is untenable, we will handle missing data with a pattern mixture model. Where we have missing data on individual variables for more than 15% of observations, we will impute using SAS PROC MI and PROC MIANALYZE to combine the results of PROC MI.

Generalized linear models (GLMs) and generalized linear mixed-effects models (GLMMs). We will assess treatment effects by using GLMs to examine differences between the intervention and EUC groups at specific assessment waves and GLMMs to examine the primary dependent measures over the study period as a whole. GLMMs have the advantage of: 1) adjusting variances for correlated data (i.e., repeated measures); 2) allowing time-varying independent variables; and 3) allowing subject-specific inferences. The link function for GLMs and GLMMs will be based on the distribution for each outcome. We will use procedures SAS PROC MIXED for continuous variables and PROC GLIMMIX for dichotomous and count data.

Aim-specific analyses. All hypotheses will be planned a priori. All analyses will use two-sided tests.

Aim 1 analyses. Hypothesis 1: Participants randomized to the intervention condition will report fewer overdose risk behaviors than EUC participants at follow-up. The overdose risk behavior is conceptually a composite count of number of behaviors. However, prior to initiating modeling, we will examine the distribution of responses to individual items on the overdose risk behavior assessment as well as the distribution of the overall composite count. Primary analyses will consist of GLMs to examine group (Intervention vs. EUC) as the primary independent variable at each time point and a GLMM to examine the average effect of the intervention over all assessments. If GLM findings suggest that the impact of the intervention may vary by assessment period, this will be examined using a time by group interaction term.

Aim 2 analyses. Hypothesis 2a: Participants randomized to the intervention condition will have lower average MEM/day doses and MPRs than EUC participants over follow-up. Hypothesis 2b: Participants randomized to the intervention condition will report lower levels of aberrant OA use than EUC participants over follow-up. Aim 2 dependent variables will include both objective measures based on pharmacy data and self-reported aberrant use. Prescribed OA dose will reflect escalating doses (likely due to patient request) and high total doses after combining regularly scheduled and "as needed" OAs.[12] An MPR[82] greater than 1 identifies potential overuse based whether new fills frequently occur before the days supplied by a prior fill have elapsed. The distribution of the daily dose, MPR, and COMM scores will be examined to select appropriate models. The same analysis strategy used to test intervention effects in GLMs and GLMMs for Aim 1 will be used for the dependent variables in Aim 2.

Secondary aim 1 analyses. Hypothesis 3: Participants randomized to the intervention condition will have fewer non-fatal overdoses, fewer injuries and other OA-related adverse events, *and better OA storage and disposal behaviors* and better functioning than EUC participants. Analysis will follow the general GLM and GLMM framework used in the Aims 1 and 2 analyses, but a survival analysis approach using Cox proportional hazards regression modeling will also be used to examine time-to-event data (non-fatal overdoses and emergency department visits).

Secondary Aim 2 analyses. Hypothesis 4a: The effect of the intervention on overdose risk behaviors and OA use will be mediated by post-intervention self-efficacy and motivation to change. Hypothesis 4b: OIF/OEF/OND status and baseline psychiatric distress will moderate the effect of the intervention on overdose risk behaviors and OA use. *Mediators:* In further analysis of the GLMs and GLMMs developed for Aims 1 and

2, we will include potential mediators in additional models and examine changes in effect size for the group indicator. Following the recommendations of Preacher and Kelley[103], we will use a κ^2 statistic to estimate the effect size and conduct significant testing of the mediation. *Moderators:* An interaction effect between each hypothesized moderator and the group indicator (intervention vs. EUC) will be specified in separate GLMs. For longitudinal analysis, we will examine baseline moderator by group interactions in GLMMs.

Additional analyses. We will examine descriptive statistics of the "perceived satisfaction and utility" measure from the post-test for further refinement of the intervention materials for follow-up. Descriptive statistics will also be used to examine differences between those who participated and those who refused participation of select characteristics. The focus group interviews conducted with prescribers will be entered into NVivo 10. Dr. Bohnert and the coordinator will independently read transcripts and use an iterative process to develop a coding scheme. Final codes will be grouped conceptually into meaningful themes and sub-themes. We will also calculate the number needed to treat to prevent one adverse event and amount of therapist time needed to prevent one adverse event.

Power analysis. All power analyses are conservative because they are based on a retention rate of 80%, n=360 (180 per condition), despite the fact that the methods will maximize analytic sample size by including individuals with partial follow-up data. All power calculations were based on two-sided tests with α=0.05 and were conducted using G*Power software. We estimated power for GLMs for both count and continuous outcomes. For continuous outcomes, such as OA dose and aberrant use (Aim 2), 80% power is achieved to detect a standardized effect size of 0.30. For overdose risk behaviors (Aim 1), we assumed a Poisson distribution and a mean count of 1.9 (based on our pilot work) and found 80% power is achieved to detect an incidence rate ratio of 0.80 for the intervention compared to EUC. We extrapolate from the power calculations presented here for GLMs that power for outcomes in GLMMs will allow for detection of similar effect sizes. Thus, the proposed study has sufficient sample size to detect small to moderate effects.

DISSEMINATION PLAN

Several dissemination products will be developed during this study. We will finalize the intervention training manual and develop additional materials. We will create a video demonstration of the different components of the intervention, with multiple examples for each component in order to show how the intervention is tailored. These products and the computer aid will be shared with key central office stakeholders and made available to VHA clinicians. Additionally, these products will be ready to be used in a future hybrid type-1 implementation study using a stepped wedge design and informed by the Replicating Effective Programs model.[104] This study could examine factors that facilitate implementation as well as fatal and non-fatal overdose as an outcome by implementing the intervention with larger numbers of patients.

The study investigators are ideally positioned to disseminate study findings to VA policymakers, VA researchers, and clinicians. Drs. Bohnert, Ilgen, and Bair are involved in the VA Pain Management Research Working Group, led by Dr. Robert Kerns. Dr. Kerns is also the Research Liaison for the VHA Program for Pain Management and also the Director of the Pain Research, Informatics, Medical comorbidities, and Education (PRIME) Center (see support letter). Study investigators will disseminate during the working group's monthly calls. Additionally, Dr. Bohnert has presented a highly-attended HSR&D Cyberseminar on the topic of overdose as part of the "Spotlight on Pain Management" series; this avenue will be used to disseminate findings to VHA clinicians, researchers, and leaderships.

Drs. Bohnert and Bair have on-going communications with Francine Goodman, PharmD of VA Pharmacy Benefits Management (PBM) Service and VA MedSAFE. This relationship has previously resulted in the direct dissemination of a study on overdose among VHA patients[12] to Dr. Goodman, who relayed the study findings to other PBM, National Pain Management, and MedSAFE leadership, which resulted in new prescribing recommendations and provider education efforts.[17] We will disseminate results to PBM and MedSAFE in order to inform VHA efforts. We will also work with the PC-MHI program office staff located in the study facilities to disseminate findings through PC-MHI online trainings and other venues. A written summary of findings will be disseminated to key system planners in VA Central Office at the end of the study.

Drs. Bohnert and Ilgen collaborate routinely with Dr. Jodie Trafton, the Director of the Program Evaluation and Resource Center, an evaluation center in the VHA's Office of Mental Health Operations (OMHO) that is closely involved in pain-related evaluation efforts. Drs. Blow, Ilgen, Pfeiffer, and Bohnert also have ongoing collaborations with the co-located Serious Mental Illness Treatment Resource and Evaluation Center, another OMHO evaluation center. Through these activities, the investigators have also generated a

number of VA clinical advisory memos summarizing research and evaluation. We will build on these connections to also work directly with VA OMHO (as well at the Office of Mental Health Services [OMHS]) staff during and after this project to ensure that the findings relevant to the provision of treatment by clinicians with mental and behavioral health training (i.e., PC-MHI staff) are disseminated. Project results will also be circulated through submission of the project's final report to the HSR&D Service, manuscripts published in peer-reviewed scientific journals, and presentations at national VA and non-VA conferences.

PROJECT MANAGEMENT PLAN

This study is based on the ongoing collaborations between two HSR&D Centers of Excellence: the Center for Clinical Management Research (CCMR) in Ann Arbor, MI and the Center on Implementing Evidence-Based Practice in the Richard L. Roudebush VA Medical Center in Indianapolis, Indiana. The data collection will be conducted in Ann Arbor VAMC research space, community locations, over the phone or through mail. Dr. Bohnert, located in Ann Arbor, will have primary responsibility for the overall management of the project. All investigators and the study coordinator will participate in biweekly meetings (with Dr. Bair attending by telephone) during data collection. The PI and coordinator will update the team on study progress and solicit feedback. The PI and coordinator will have weekly meetings with staff to ensure fidelity to study protocols and discuss issues as they arise, with involvement from study Co-Investigators on an as-needed basis. Additionally, all investigators will meet once in person in Ann Arbor to refine the final study protocol within the first four months of funding.

The project will take four years to complete. The first year will be used to hire and train research staff, conduct focus groups with primary care physicians, develop and refine the protocol for notifying prescribers when their patients indicate acute and serious risk of self-harm, establish a patient advisory panel, finalize intervention and control materials, pilot the intervention with a small number of patients, and obtain final IRB and R&D approval for all study procedures and protocols. From month 8 of year 2 through month 6 of year 3, participants will be recruited into the study, complete baseline assessments, be randomized to the intervention or control conditions, and complete the relevant protocols. Follow-up assessments will continue until year 4, month 6. The last six months will be used to finalize analyses, develop dissemination products, and disseminate findings.

HUMAN SUBJECTS

1. Risk to Subjects

Human Subjects Involvement and Characteristics

The proposed study will be a randomized controlled trial of a brief, tailored motivational enhancement (ME) intervention with cognitive behavioral elements to reduce opioid overdose risk behavior for patients in the VHA primary care setting who are receiving moderate to high doses of opioids. The proposed study will recruit patients (N = 450), ages 18 and older from primary care (PC) clinics at the VA Ann Arbor Healthcare System in Ann Arbor, Michigan. Patients with long-term opioid use, defined as at least 84 days covered within the past 90 days, and who are currently prescribed doses of 20 morphine-equivalent mg/day or greater will be screened and recruited into the study. Participants will then be randomized to either the intervention (n = 225) or an equal-attention enhanced usual care condition (n = 225). Pharmacy records and patient self-report will be assessed at baseline and 3-, 6-, and 12-month follow-ups to measure key outcomes.

Inclusion criteria: Data will be collected from patients who: 1) are 18 years of age and older; 2) understand English; 3) are able to provide informed consent; 4) receive treatment at primary care clinics at the Ann Arbor VA Medical Center; and 5) are prescribed 20 morphine-equivalent mg daily or more of an opioid as part of long-term opioid therapy (defined at least 84 days covered within the past 90 days).

Exclusion criteria: Patients will be excluded if they: 1) plans to stop OAs or reduce dose to below 20 MEM/day in the next 6 months, 2) use of fentanyl, due to the difficulty in determining morphine equivalency (preliminary work indicated that less than 2% of VHA patients receiving OAs are prescribed fentanyl), 3) only opioid type used is Tramadol/Ultram because it is not subject to the long-term OA therapy informed consent process 4) prescribed or using Suboxone, 5) terminal cancer, 6) acute risk for self-harm related to opioid use requiring

immediate treatment (see next section), which is then likely to result in a reduction or cessation in opioid therapy, 7) moderately severe cognitive impairment (based on a validated six-item cognitive screener[76]) to ensure accuracy of data, 8) pregnant women, and 9) inability to give informed consent. Participants may be included or excluded at the discretion of the Principal Investigator.

Sources of Materials
Patients treated in the primary care clinic will initially be screened via medical records data and logs of the patients scheduled for appointments; this will be done using methods that have been IRB-approved and deemed HIPAA-compliant in our prior work. Screening based on medical records will include diagnoses and opioid prescribing from medical visits occurring in the prior 3 months. Research staff will then create a list of potentially eligible patients with appointments on a weekly basis. We may send a letter to those patients selected to be approached in advance of their appointment, which will briefly describe the study and provide a number to call to "opt out" of being approached.

In coordination with the study analyst, the research staff will then apply a random sampling schema to the list of potentially eligible participants and approach those selected, who have not previously opted out. The patients' documents for the visit will indicate their eligibility so that their provider can remind them that they may be approached to participate in a research study, consistent with IRB-approved processes in ongoing studies at the study site. Participants who are not able to stay after their medical appointment will be allowed to schedule an appointment with the study staff for a time before or after a future medical appointment to return and hear about the study, provide informed consent, and answer additional screening questions verbally. Participants with limited time will be given the option to complete the informed consent process in-person, then follow-up with a phone call to complete the survey assessment and intervention. This will be used as a last resort for those participants who have restricted availability or concerns with travel. Participants who chose this option will be able to complete the urine drug screen in-person after completing the informed consent document. The additional screening questions will include a determination of: 1) whether the potential participant has stopped taking or plans to stop taking their opioid medication; 2) whether the potential participant plans to reduce their opioid dose to below ≤ 20 morphine-equivalent mg per day in the next six months; 3) a brief screener of cognitive impairment; and 4) the presence of any other exclusion criteria not noted from the medical record.

Participants meeting inclusion criteria for the trial will complete a baseline assessment and be randomized either to the intervention or to an equal-attention enhanced usual care (EUC) condition. The study research assistant will re-assess participants at 3-, 6-, and 12-months post-intervention/EUC. Participants will be re-assessed at these time points post-baseline to detect changes in overdose risk behaviors, prescription opioid use and aberrant opioid use, non-fatal overdoses, and other medication-related adverse events. Additional objective data will be obtained using clinical records and urine drug screens.

Potential Risks
<u>Loss of confidentiality (unlikely, serious):</u> The major potential risk to study participants is violation of confidentiality due to participants' disclosure of sensitive personal information (e.g., substance use history) during the study and the harm that could be caused by inadvertent release. The investigative team has considerable experience in maintaining the confidentiality of large datasets and has established procedures in place to ensure data confidentiality. All investigators and research staff have met training requirements for handling protected health information as outlined by the Health Insurance Portability and Accountability Act (HIPAA). For this study, we will request a HIPAA waiver of informed consent for access to protected health information in order to determine which participants are eligible to be approached. The proposed research qualifies for this waiver because it involves no more than minimal risk to the subjects and the waiver will not adversely affect the rights or welfare of subjects. In addition, the research could not practicably be carried out without the waiver or alteration. In order to be granted a waiver, we will need to demonstrate procedures (outlined below) that protect patient identifiers from improper use and disclosure.

<u>Discomfort during assessments (likely, moderately serious):</u> There is also the risk of psychological discomfort among study participants as a result of being asked personal questions on sensitive topics. Because some

participants may experience distress when answering these questions, they will be made aware of their right to refuse to answer any questions that make them uncomfortable or that they do not wish to answer, and will be informed of their right to withdraw from the study at any time without penalty. Additionally, study staff will be trained extensively to respond to emotional distress and to discuss concerns and issues if they arise. Crisis procedures, effective in previous projects conducted by the study investigators, will be utilized.

2. Adequacy of Protection from Risk

Recruitment and Informed Consent
Prior to implementation, the study consent forms, like all research procedures and documents, will be approved by the Institutional Review Board (IRB) of the VA Ann Arbor Healthcare System. Potential participants will be recruited from the VA Ann Arbor Medical Center primary care clinics. We may send a letter to those patients selected to be approached in advance of their appointment, which will briefly describe the study and provide a number to call to "opt out" of being approached. Patients who have not "opted out" will be approached by the research staff and asked to participate in the screening portion of the study.
Additionally, study flyers will be posted around the primary care clinic, physical therapy clinic, and other related clinics in the Ann Arbor VA. The flyers will mention our study and provide our study contact number for participants to find out more information. Similar to our current protocols, we will confirm a patient's eligibility through review of pharmacy, Opioid Therapy Risk Report, and chart review. The Primary Care-Mental Health Integration (PC-MHI) staff and providers will be given flyers that they may distribute to appropriate patients. They will not be involved in the recruitment of participants, other than handing out flyers. While this will expand our recruitment efforts, we will emphasize that the PC-MHI staff will only provide the patients with the flyer. The flyer will introduce the study and provide contact information. Study staff will confirm that any interested patient's involvement in the study will not affect their primary care or VA treatment. Their involvement is completely voluntary.

Study staff will conduct initial screening of participants (after obtaining a HIPAA waiver of informed consent for recruitment purposes) in conjunction with the data analyst via medical records and logs of the patients scheduled for appointments using methods that have been IRB-approved and deemed HIPAA-compliant in our prior work. Screening from medical records will include opioid prescribing from medical visits. Medical records will also be used to determine whether a terminal cancer diagnosis is present. Staff will then create a list of potentially eligible patients with appointments on a weekly basis. This list will be compared against study files in order to avoid approaching already enrolled participants or individuals who have already refused participation. Medical records data will not be retained after this list is generated.

In coordination with the study analyst, the research staff will then apply a random sampling schema to the list of potentially eligible participants and approach those selected. Medical records data will also be used to determine basic demographic and diagnostic information for individuals who are not selected through randomization, refuse participation, who "no-show" for their baseline assessment, or who are missed by study therapists (using methods deemed HIPAA-compliant in our prior work) in order to assess generalizability of the study sample.

Study staff will approach potentially eligible participants individually while those patients are waiting for appointments or after their appointment ends and will describe the study briefly. Study staff will escort interested participants to an area where privacy and confidentiality can be maintained after the completion of their medical appointment in order to conduct informed consent and additional screening procedures, including the cognitive status exam. Privacy during assessments will be achieved by making sure no one can overhear the conversation. If applicable, we will ask the research subject to have others leave the room during interviews. Study staff will do everything within their capacity to ensure that participants' privacy and confidentiality is maintained during every interaction with participants. Study staff will speak in low tones and pause or move if someone who is not on the study team enters the area. Participants who are not able to stay after their medical appointment will be allowed to schedule an appointment with the study staff to return and hear about the study, provide informed consent, and answer additional screening questions. Participants will be given the option to complete their interview or baseline survey at that time or complete the survey within 5-10 days. We will seek to recruit those participants who refuse to participate in the randomized controlled trial to participate in a five-minute survey to better understand how those participants differ from those that do participate on key factors and their reasons for refusing participation.

The screening survey will commence after the participants provide written informed consent. Research staff will inform participants of the general nature of the study, expectations for and the voluntary nature of their participation, and that their participation can be withdrawn at any time. When providing written informed consent, participants will be given a copy of the consent form.

Protection Against Risk

To minimize the risk of breaches of confidentiality, every effort is made to ensure that study data are always confidential, and never stored so that data can be linked to a particular person. Research staff will sign a pledge of confidentiality and be informed that breach of confidentiality is reason for dismissal. Training of staff will include information about the importance of confidentiality and techniques to maintain confidentiality of all information reported by research participants. Further, all staff will be required to complete VA trainings in human research study protections and provide documentation of VA confidentiality certification. Unique identification numbers will be assigned to participants. All data forms, transcripts, and electronic audio recording files will be coded with this number rather than with a name. All paper forms will be stored in locked file cabinets. Electronic data files will be stored on a secure server with restricted access. Consent forms and "Participant Directory" sheets will be stored separately, because they contain identifying information (due to the need to re-contact participants for follow-ups). Prior to data entry of follow-up information, all identifying information will be removed from follow-up interviews. Only the participant code number will be entered with study data. Furthermore, we will apply for a Certificate of Confidentiality from the NIH to protect the confidentiality of data from legal requests.

Research staff will be available following participation in all screenings and assessments to manage (i.e., discuss and refer as needed) any unexpected issues that may arise. These include increased distress or feelings of discontentment that answering questions may have caused. In addition, research staff will provide referrals as needed.

It should be noted that although the focus of this study is not on child abuse or intention to harm others, because of the nature of this study, these issues could arise. Additionally, intent to harm oneself (or serious imminent risk of self-harm without suicidal intent) will be assessed as part of the study. The consent form will contain a statement explaining the mandatory reporting requirements for information regarding child abuse and intention to harm self or others as well as the protocols for informing the participant's opioid prescriber in the event of serious, imminent risk of self-harm with opioids that will be developed during the study start-up. The recruiter will discuss this with potential participants during the informed consent process. Staff training will include a review of the study protocol regarding the limits of confidentiality, how to liaison with study site staff (i.e., psychiatry, crisis management) to arrange for an assessment, circumstances in which it may be necessary to notify authorities regarding intent to harm self or others, and the development of safety plans and resources. Study procedures also will include immediately paging Drs. Bohnert, Pfeiffer, or Ilgen in cases in which this may arise.

3. Potential benefits of research to subjects and others

The questions addressed by this study, regarding high prescribed doses of opioids, non-medical opioid use, opioid safety, and overdose risk, have considerable public health and treatment implications. While patients involved in this research may not derive any direct individual benefits from participation, the study may identify strategies for reducing opioid-related overdose risk behaviors, and all patients may benefit from intervention and EUC educational content on opioid safety. Additionally, others may ultimately benefit from the knowledge obtained in this research project, as these findings may inform clinicians on how to better intervene with patients to reduce risk for opioid-related adverse outcomes. In light of the precautions that will be taken to ensure data security, it is likely that the benefits of this study outweigh the potential risk.

4. Importance of knowledge to be gained

Opioid medications have been increasingly used in the treatment of pain in the U.S, and there have been parallel increases in adverse consequences related to opioid treatment, particularly overdose. However, ways to reduce risk of these adverse consequences are not well understood. Consequently, data on how a brief overdose prevention intervention for primary care patients prescribed long-term opioid therapy at

moderate to high doses are crucial to collect. With the information obtained from this study, providers may be able to provide a novel intervention to reduce adverse outcomes among their patients with pain. This study would be the first to our knowledge to examine such an intervention using randomized controlled trial procedures. Given the minimal risks to the subjects, the risk to those participating is reasonable in relation to the importance of the knowledge to be gained.

5. Data and Safety Monitoring Plan

Data Monitoring Plan
The Principal Investigator, Dr. Bohnert, ultimately will be responsible for monitoring the data safety and quality with involvement from all of the study investigators. Data will be collected using paper-and-pencil surveys, and audio recording devices and will only be identified with the study IDs of the participant. The codes that link the name of the participant and the study ID will be kept separately and securely.

Quality control and reliability of baseline and follow-up assessments will be monitored by Dr. Bohnert and the study coordinator throughout the study via regular meetings, listening to and coding therapist audiotapes of the intervention, and data quality checks of the assessments. Ms. Ganoczy, the study data analyst, will monitor the quality of the quantitative data files.

The electronic files, paper-and-pencil study documents, and/or audio recordings will be securely uploaded or entered to a restricted access file behind a VA firewall. Data collected via hard copy will be entered in the computer independently by trained data entry staff, and discrepancies will be corrected by a supervisor, based on source documents. The letter that will be sent with mailed surveys reminds participants not to include any identifiable information on their survey to ensure privacy and confidentiality. The quality of the data will be monitored by random inspection of the completed forms by the research coordinator or trained RA and any problems detected will be discussed with the PI. Blind interim analyses of the data will be conducted at two points - when 50 and 75% of the sample has been accrued. The PI and study data analyst will analyze the data.

<u>VA Informatics and Computing Infrastructure (VINCI)</u>
We may request data extracts from the VHA Corporate Data Warehouse (CDW). VINCI is a partner with the Corporate Data Warehouse and hosts all data available through CDW. As VA and VHA research progresses, large amounts of data are being collected into databases maintained by a variety of investigators, studies, and locations. Individual investigators and multiple databases may lack sufficient resources to ensure consistency and quality control, or a long-term commitment to data storage and access. Therefore, there are less consistent standards for the protection of Veterans data, data quality, and data access compared to a centralized repository. A centralized research data repository, such as the VA Informatics and Computing Infrastructure (VINCI), offers a number of important advantages: Consistent, defined, and transparent security and standards for access to data; a common point of entry for all investigators who use the data; tools for analysis and reporting; tighter and more consistent control over the standards and quality of the data included; and the ability to standardize and update terminology and format as technology and methodology improve. VINCI is a partnership between the VA Office of Information Technology (OI&T) and the Veterans' Health Administration Office of Research and Development (VHA ORD). VINCI provides the storage and server technologies to securely host suites of databases integrated from select national data. These servers reside at the Austin Information Technology Center (AITC), located in Austin, Texas. To ensure the protection of Veterans data, VINCI maintains compliance with the guidelines set forth by Veterans Health Administration (VHA) Handbook 1200.12, Use of Data and Data Repositories in VHA Research and all other applicable VA and VHA policies and regulations. In addition, VINCI has undergone all security certification activities in support of obtaining an Authorization to Operate (ATO). Access to VINCI resources will be approved in accordance with the requirements of National Data Systems (NDS), VHA Handbook 1200.12, Use of Data and Data Repositories in VHA Research, and all other applicable VA and VHA policies and regulations. Researchers and Operations staff will access the data along with the tools for analysis and reporting in the secure, virtual working environment through a certified VHA network computer using the VA INTRANET (NOTE: VINCI is not accessible through the INTERNET). If not working within a VA or VHA hosted office

environment containing VA network access, researchers may access VINCI through an approved Virtual Private Network (VPN) and Remote Desktop application. The remote computing environment will enable data analysis to be done directly on VINCI-CDW servers located at the Austin Information Technology Center, thus keeping all data from being transmitted to local PC hard drives.

VINCI Data Collection

VA provides care to veterans at over 1,400 points of care. At the core of virtually all care processes is a broadly scoped and extensively used electronic health record system known as the Veterans Information System Technology Architecture (VistA). VistA provides a longitudinal view for patients receiving care nationwide including diagnosis, procedures, pharmacy, orders, labs, microbiology, physiologic measurements, and text documents. VA uses 128 VistA implementations to provide longitudinal electronic health record services nationwide for more than 25 million veterans historically. The aggregate content of these 128 VistA systems includes just over 1.03 Billion documents (e.g., Progress Notes, Discharge Summaries, Reports) accumulating at a rate of 638,000 each workday; 1.65 Billion orders (+955,000 each workday); 590 Million images (+884,000 each workday); 1.06 Billion vital sign measurements (+729,000 each workday) and 850 Million medication administrations (+607,000 each workday).

VA Informatics and Computing Infrastructure (VINCI) aggregates data sources from individual VistA systems, data from the Regional Data Warehouses for all 4 VA regions, the VA Corporate Data Warehouse, and the VA Health Data Repository and prepares them for research use. Other data published by the VHA Decision Support System (DSS) and Inpatient and Outpatient Medical SAS (MedSAS) can be requested through VINCI. VA National Data Services and other data stewards regulate the right to use the data, but VINCI facilitates the process. VINCI servers for data, applications and virtual sessions are physically located in the VA Automation Center in Austin, Texas. This secure enclave with 20 racks of high-performance servers and 72 terabytes of high-speed data storage has multiple layers of security to prevent data loss. When study data requested through VINCI is approved for use, it is extracted from source databases and placed in SQL tables accessible only to the research team and VA Automation Center OI&T operations personnel.

VINCI Natural Language Processing (NLP)

The VINCI application library has a suite of Natural Language Processing (NLP) tools for extracting information from unstructured text. The ability to create textual reports offers flexibility to clinicians for describing symptoms, vital signs, behaviors, attitude, instructions, patient and family history, and much more; but free text is not a data format well suited to the analytical tools familiar to researchers.

VINCI has an NLP “Pipeline”, a collection of configurable NLP modules available as a Service Oriented Architecture (SOA) within the VINCI processing environment. This SOA pipeline, named V3NLP, is more easily configured than other NLP pipelines and it is easier to adapt existing GATE or UIMA NLP modules to the SOA environment. VINCI and their customers have adapted V3NLP to data patterns specific to the VA and V3NLP has been used for several clinical use cases.

Opioid Therapy Risk Report (OTRR)

The OTRR tool is developed by the VHA Support Service Center (VSSC). Corporate Data Warehouse (CDW) extracts data from every local VistA system every 24 hours and transforms it into a National repository used to create the OTRR. Due to the sensitive nature of the data involved, the system validates the security credentials for everyone accessing the OTRR to ensure they have authorization to view patient PHI/PII. The check is transparent to the user. If the check determines the user does not have authorization to view patient PHI/PII, a notification will appear. OTRR Activities are audited and include details such as who accessed the system, when, where, and what parameters they selected. Using the OTRR format that displays the minimum data needed to carry out responsibilities is another way of supporting security.

Research staff will access the OTRR tool through a secure intranet VA website. The research team has IRB approval for temporary access to protected health information for screening purposes. Study members have confirmed that they have Station Level Access, which is required for accessing VSSC tools. The data will be extracted for only Ann Arbor (506) patients. OTRR can be downloaded to our local VA server on a weekly basis to check for potential participants with upcoming appointments that meet our inclusion criteria. Only those on our study IRB will have access to this tool for this study.

Safety Monitoring Plan

Study applicants will be thoroughly screened to determine their eligibility and safety for their participation in this study. Special attention will be placed on history of suicidal ideation or suicide attempts, measured by the questions taken from the National Comorbidity Survey and overdose history. Any indication of acute suicidality will be further assessed in-depth by the therapist or research associate in consultation with Drs. Bohnert, Ilgen, or Pfeiffer. Participants determined to be at significant risk will be referred to their regular provider or the clinic's crisis management team, who will make decisions about additional treatment.

It has been our experience that some patients who report a recent suicide attempt or moderate suicidal ideation who are currently being managed by a mental health provider are able to successfully participate in surveys and interviews. Research staff will explicitly discuss the potential risks inherent in research involvement and the participant's concerns about involvement with those participants who endorse mild or moderate suicide ideation. This information, in combination with the patient's medical records and self-report, will help the research staff to make his/her decision regarding study eligibility. If any of these determinations are unclear, he/she will consult with the supervising psychologist (Dr. Ilgen) or psychiatrist (Dr. Pfeiffer), both of whom have research and clinical expertise in suicide risk management, for a second opinion. Participants who report acute suicidality will not continue with assessment procedures and will be referred to same-day care through either a Primary Care-based Psychiatrist or the VAAAHS emergency department, in compliance with human subject protections procedures, or will be referred to the same locations or to specialty mental health if the treatment needs are non-urgent. Those participants in the trial who report acute suicidality at a 3- or 6-or 12-month follow-up assessment will be assessed for imminent risk and connected to the appropriate type of mental health services. Research staff will attempt to contact at least three times within 72 hours participants who flag for risk (suicide or opioid) in with mailed follow-up assessment. Mailed follow-up assessments will include an insert that alerts the participant that this survey is not a way to reach out for help regarding suicidal ideation or thoughts. It will include the Veterans Crisis Line number and inform the participant that if they indicate suicidal thoughts or ideation that the research staff will follow-up once the survey is received.

In the course of study participation, including the assessments, intervention, or EUC activities, it may be determined that a participant is at acute risk for serious self-harm related to their opioid use. Study staff have been trained to include in the exclusions of confidentiality, self-harm not only in terms of suicide but also related to participant's opioid prescription. Participants will be notified that research staff may discover opioid self-harm risk from the survey, intervention session or general discussion with the participant. When this risk arises, study staff will discuss this risk with the patient and discuss that the provider will be informed. The participant will be given the option to disclose this to their provider, with the study staff in the room, when possible. Study staff will notify the participant's prescriber in the situation where the participant does not, or the provider is not available, based on protocols that were designed in consultation with opioid prescribers through focus groups and primary care staff meetings. The discussion between study staff and provider will only discuss the relevant information (e.g., mentioned use of cocaine, endorsed using heroin, etc.), but will not make any clinical conclusions or suggestions. Study staff will also make additional referrals as needed. During data analysis, we examine any impact through a sensitivity analysis. Additionally, we will notify all participants' prescribers that the participant is at risk for overdose due to their medication regimen and/or OA use behaviors. The notification will include the fact that we will have discussed this risk with the patient. This will be done for both intervention and control participants to avoid potential differential effects on the measurement.

Drs. Bohnert, Ilgen, and Pfeiffer will be responsible for providing training to all research staff working with participants at the study site with regard to procedures for managing issues that could arise given the patient population, including potential crisis situations and/or adverse events. Given the population under study, it is expected that participants may report current suicidality. Specifically, this training will include information regarding evaluating warning signs of acute suicidal ideation, planning, or intent, and means of addressing such issues. Research staff will be trained in crisis procedures including limits of confidentiality, how to liaison with study site staff (i.e., treatment providers, crisis management) to arrange for an assessment and potential admission for inpatient care, and circumstances in which it may be necessary to notify authorities regarding intent to harm self or others. The crisis procedures also will include immediately paging Drs. Bohnert or other clinical staff for consultation and conference call discussions with other investigators as necessary.

Additionally, research staff will be trained to use certain strategies should participants express emotional distress such as: intervening early, avoiding blame, increasing empathy, processing in a non-blaming non-confrontational manner, and taking a break in the session if necessary. The training manual will contain written procedures for dealing with such situations and will include a detailed, ordered list of phone numbers (i.e., home, work, cell, pager) to facilitate immediate contact with investigators.

For individuals that trigger the need for a suicide assessment, research staff will inquire about plan, severity, and risk factors. Drs. Bohnert, Ilgen, or Pfeiffer will be contacted for individuals that are at high risk (i.e. distinct and/or immediate plan to harm oneself). Staff will consult with the supervising psychologist (Dr. Ilgen) or psychiatrist (Dr. Pfeiffer), both of whom have expertise in assessing suicide risk. Drs. Ilgen, or Pfeiffer will make a decision about appropriate next steps, including the need for emergency or follow-up evaluation, requesting the participant to contact a family member or friend, contacting a facility/hospital staff member (i.e., psychiatrist on call, participant's provider) before the study staff member leaves the location, performing a warm handoff with the Veterans Crisis Line, contacting local authorities, etc. If Drs. Ilgen or Pfeiffer indicate the level of risk suggests the need for a professional or emergency evaluation, the study staff member will assist in facilitating the next step. All participants will be given mental health referral information.

Study Specific Plan for Reporting Adverse or Other Reportable Events or Information
Given the characteristics of the study population (participants prescribed high doses of opioid pain medication), we will create a study specific adverse event reporting plan. We will report all AEs that are **unexpected and directly related** to the study (except as noted in the first row of the table below). "Unexpected" means that the event has not been addressed or described in the informed consent document, protocol, data and safety monitoring plan, and/or is not a characteristic of the study population. "Related" means events that are caused by the research itself, not the disease or population under study. Unexpected events that are not directly related to the study will not be reported (see examples in table), with the exception of participant death.

The person responsible for reporting adverse events will be Dr. Bohnert. In addition, Dr. Bohnert will ensure that all relevant VA IRB policies, procedures and stipulations are being followed. Dr. Bohnert will also be responsible for ensuring that other investigators and project staff adhere to the VA IRB policies including: (1) All participants will understand, agree to, and sign a written consent form before participating; (2) Strict adherence to a participant's right to withdraw or refuse to answer questions will be maintained; (3) The assessments will be completely confidential and no names will be associated with the assessment data; (4) Consent forms and identifying information will be kept separately from the actual participant data; (5) All identifying information will be kept locked at all times and computer files will have restricted access; (6) Participants will be informed in writing in the consent form how to contact the PI with any questions and/or concerns. The study coordinator will compile information of adverse events, UPRs, and SAEs on an ongoing basis. On a quarterly basis during the period of active recruitment and follow-up, the coordinator will report this information to the PI and the other study investigators at study meetings meant to monitor study progress. In advance of this meeting, the PI will review these data with the coordinator so that any additional information needed to evaluate the monitoring plan can be obtained prior to the meeting.

The table below is included to outline what are expected events specific to our study:

Type of Event	Examples	Reporting Timeframe
Expected and **Study-Related** *Serious* Adverse Events	▪ Hospitalization as a direct result of study interaction resulting from report of self-harm thoughts or behaviors (e.g., acute opioid risk, or suicidal).	Reported in accordance with IRB guidelines

Expected and **Study-Related** Adverse Events	▪ Participants reporting self-harm thoughts or behaviors ▪ Breach of confidentiality associated with reporting self-harm to agency staff, appropriate authorities, and/or mental health personnel. ▪ Discomfort associated with answering survey questions/discussing intervention topics.	Not reported to IRB
Expected and **Not Study-Related** Adverse Events and *Serious* Adverse Events	▪ Emergency room visit related to self-harm or substance use/overdose ▪ Hospitalization for suicidal thoughts or substance use/overdose ▪ Social or psychological trauma related to substance use	Not reported to the IRB
Expected protocol deviations/exceptions	▪ Missed appointments and/or sessions. ▪ Breach of confidentiality associated with reporting suspected abuse to Child or Elderly Protective Services.	Not reported to IRB
Unanticipated Problem Involving Risks to subjects or Others (UAP) – Serious and Non-Serious		Reported in accordance with IRB guidelines

6. Inclusion of Women, Minorities, and Children

Inclusion of Women
Of the 450 Veterans recruited to participate in this study, we expect that about 5.5% (N = 24) will be women, based on the overall prevalence of female gender among patients treated with opioids in primary care at the VAMC. Pregnant women will not be included in the study.

Inclusion of Minorities
Of the 450 Veterans recruited into this study, we expect that the sample will consist of 1.5% Hispanic or Latino/a Veterans. Regarding race, we expect that 9.8% will be Black or African American, 88.5% White, 0.8% American Indian or Alaskan Native, 0.5% Asian, and 0.4% Native Hawaiian or Other Pacific Islander.

Inclusion of Children
This project will not include children. Individuals age 17 years old and under will be excluded due to the study focus of pain management in VHA primary care among Veterans. These veterans will be at least 18 years old. Notably, pain conditions are relatively uncommon among children as compared to adults; however, due to biological, psychosocial, and developmental differences between these age cohorts, even those children with

pain conditions likely require dissimilar approaches to pain management and adverse event risk management compared to adults. Based on these differences, a separate study would be required to appropriately examine opioid safety among children and adolescents with pain conditions.

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