Engaging Veterans Seeking Service-Connection Payments in Pain Treatment

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Study Protocol

National Center for Complementary and Integrative Health

FULL PROTOCOL TITLE

Engaging Veterans Seeking Service-Connection Payments in Pain Treatment

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Version 4.0

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Version Number: 4
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Summary of Revisions Made: Change to operationalization of substance use outcome

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ABBREVIATIONS

AE:	Adverse Event
ASSIST:	Alcohol, Smoking and Substance Involvement Screening Test
ATO:	Authorization to Operate
AUDIT-C:	Alcohol Use Disorders Identification Test
BPI:	Brief Pain Inventory
C&P:	Compensation & Pension
CAPRI:	Compensation and Pension Record Interchange
CBT:	Cognitive Behavioral Therapy
CDC:	Centers for Disease Control and Prevention
CEACs:	Cost-Effectiveness Acceptability Curves
CIDI:	Composite International Diagnostic Interview
cIRB:	Central Institutional Review Board
COVID-19	Coronavirus Disease 2019
CPT:	Current Procedure Terminology
CTSP:	Centralized Transcription Service Program
DBQ:	Disability Benefits Questionnaire
DSMC:	Data and Safety Monitoring Committee
EHR:	Electronic Health Record
ELISA:	Enzyme-Linked Immunosorbent Assay
ETG:	Ethyl Glucuronide
ETOH:	Alcohol
EQ-5D-5L:	5 Level EuroQol: Instrument used to Describe and Value Health
FDA:	Food and Drug Administration
HERC:	Health Economics Resource Center
HIPAA:	Health Insurance Portability and Accountability Act
HSR&D:	Health Services Research & Development
ICERs	Incremental Cost-Effectiveness Ratios
IMMPACT:	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IMPROVE:	Improving Pain-Related Outcomes for Veterans
IRB:	Institutional Review Board
ITRS:	Independent Tape Rater Scale
ITT:	Intent to Treat
JAMA:	Journal of the American Medical Association
MAR:	Missing at Random
MCAR:	Missing Completely at Random
MCID:	Mean Clinically Important Difference
MEDD:	Morphine Equivalent Daily Dose
MI:	Motivational Interviewing
MNAR:	Missing Not at Random
mPI:	Multiple Principal Investigator
MSD:	Musculoskeletal disorders
NCCIH:	National Center of Complementary and Integrative Health

NDS:	National Data Systems
NIDA:	National Institute on Drug Abuse
NIH:	National Institutes of Health
NLP:	Natural Language Processing
NPCD:	National Patient Care Database
NPM:	Non-Pharmacological Pain Modalities
NRS:	Numeric Rating Scale
OEF:	Operation Enduring Freedom
OHRP:	Office for Human Research Protections
OIF:	Operation Iraqi Freedom
OI&T:	Office of Information & Technology
PACT:	Patient Aligned Care
PEG:	Three-Item Scale Assessing Overall Pain Intensity and Interference
PMC3:	NIH-DoD-VA Pain Management Collaboratory Coordinating Center
PHI:	Personal Health Information
PHQ-9:	Patient Health Questionnaire
PPV:	Positive Predictive Values
PRC:	Protocol Review Committee
PRIME:	Pain Research, Informatics, Multi-morbidities, and Education Center
PT:	Physical Therapy
PTSD:	Post-Traumatic Stress Disorder
QUERI:	VA Quality Enhancement Research Initiative
RCT:	Randomized Controlled Trial
REDCap:	Research Electronic Data Capture
SAE:	Serious Adverse Event
SAMSHA:	Substance Abuse and Mental Health Services Administration
SBIRT:	Screening, Brief Intervention and Referral to Treatment
SBIRT-PM	Screening, Brief Intervention and Referral to Treatment for Pain Management
SCAN-ECHO:	Specialty Care Access Networks-Extension for Community Healthcare Outcomes
SPACE:	Strategies for Prescribing Analgesics Comparative Effectiveness
SUD:	Substance Use Disorder
SVM:	Support Vector Machine
TAU:	Treatment-As-Usual
TBI:	Traumatic Brain Injury
TENS:	Transcutaneous Electrical Nerve Stimulation
UG3:	Phase 1 Exploratory/Developmental Cooperative Agreement activity code
UGH:	Phase 2 Exploratory/Developmental Cooperative Agreement activity code

UC:	Usual Care
VA:	Veterans Affairs
VACHS:	VA Connecticut Healthcare System
VACO:	VA Central Office
VAMC:	VA Medical Centers
VBA:	Veterans Benefits Administration
VBMS:	Veterans Benefits Management Software
VERA:	Veterans Equitable Resource Allocation
Veterans' Choice:	Veterans Access, Choice and Accountability Act
VHA:	Veteran's Health Administration
VHA ORD:	Veterans Health Administration Office of Research and Development
VINCI:	VA Informatics and Computing Infrastructure
VISN:	Veterans Integrated Service Networks
VPN:	Virtual Private Network
VTT:	Visual Tagging Tool

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- Boston VA
- Central Western Massachusetts VA
- Maine VA
- Manchester VA
- Providence VA
- White River Junction VA

Other Sites Involved in Data Analysis

- Washington DC VA

PRÉCIS

Study Title

Engaging Veterans Seeking Service-Connection Payments in Pain Treatment

Objectives

Determine the effectiveness and cost-effectiveness of Screening, Brief Intervention and Referral to Treatment for Pain Management (SBIRT-PM) compared to Usual Care (UC) in reducing pain and risky substance use.

Design and Outcomes

In a pragmatic two-arm, parallel groups 36-week multi-site randomized controlled single blind trial, we will randomize 1100 Veterans applying for compensation related to musculoskeletal disorders to either SBIRT-PM or Usual Care (UC) across eight VA medical centers in New England.

Outcome assessment by phone will occur at 12- and 36-week follow-ups and will be corroborated with other sources of information --- the electronic health record and toxicology testing of nail clippings.

Primary outcomes will be change in pain severity as measured by the Brief Pain Inventory (BPI) and change in substances categorized as requiring intervention measured by the ASSIST. Secondary outcomes will include non-pharmacological pain management service utilization, NRS pain severity, pain interference with life activities as measured by the BPI, overall pain (PEG), overall health (EQ-5D-5L), use severity for individual substances generated by the ASSIST, and toxicology results for individual substances. The trial will include cost-effectiveness and budget impact analyses.

Interventions and Duration

Screening, Brief Intervention and Referral to Treatment for Pain Management (SBIRT-PM) aims to engage Veterans applying for compensation with pain conditions in multi-modal non-pharmacological pain care and to motivate those who misuse substances to change this problematic behavior. SBIRT-PM will be delivered centrally by telephone throughout the New England VA Healthcare System's (VISN1) eight medical centers. It involves an initial one-hour session followed by up to three 20-minute calls in a 12-week period and an additional call in the 12-32 week period to support Veterans engagement in non-pharmacological pain care.

Usual care (UC): A Veteran who completes a compensation examination ordinarily has no further treatment, referral or debriefing as part of the Compensation examination

Sample Size and Population

The study sample consists of 1100 randomized post-911 era Veterans applying for MSD related compensation. Participants will be randomized using a computerized urn randomization program within each site to increase the likelihood of balanced allocation of participants to the two interventions on

sex, race, ethnicity and self-reported illicit drug use within 90 days.

1. STUDY OBJECTIVES

1.1 Primary Objective

Our main objective is to test the effectiveness and cost-effectiveness of SBIRT-PM, compared to UC, when delivered within a VISN1-wide hub-and-spoke network.

Objective 1: We will determine if SBIRT-PM is more effective than UC in reducing pain severity as measured by the Pain Severity subscale of the BPI (primary outcome). Secondary outcomes include non-pharmacological pain management service utilization, pain interference with life activities (BPI Interference Subscale), and overall health. Hypothesis: SBIRT-PM will be more effective than UC. We will test the degree to which non-pharmacological pain management service utilization mediates pain outcomes.

Objective 2: We will evaluate if SBIRT-PM, compared to UC, is more effective in reducing the number of substances categorized as requiring any intervention as measured by the ASSIST (primary outcome). Secondary outcomes will include the use severity measure for individual substances generated by the ASSIST, and nail clipping toxicology results for individual substances. Hypothesis: SBIRT-PM will be more effective than UC. We will separately test the degree to which non-pharmacological pain management service utilization and substance use service utilization mediates the effect of SBIRT-PM on substance use outcomes.

Objective 3: We will assess the cost-effectiveness of SBIRT-PM relative to UC. Hypothesis: SBIRT-PM will be cost-effective relative to UC across a range of possible values of decision makers' willingness-to-pay for minimal clinically important differences in pain severity and interference.

1.2 Secondary Objectives

Our secondary objective is to determine if SBIRT-PM is more effect than UC in reducing overall pain as measured by the PEG, a common pain measure required across protocols funded by the NIH-DoD-VA Pain Management Collaboratory, which measures average pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G). Hypothesis: SBIRT-PM will be more effective than UC.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Many Returning Post-9/11 Veterans Have MSD and Could Benefit from Non-Pharmacologic Pain Care.

Military personnel carry heavy packs, move heavy equipment and undergo intense physical stresses; a high proportion of them will develop musculoskeletal disorders (MSD) involving chronic pain. Chronic pain is widely prevalent in Veterans and is one of the most common reasons for outpatient healthcare utilization.[1] In recent years, returning Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) post-9/11 Veterans with injuries have faced the prospect of decades of chronic pain.[2,3]

By seven years after deployment, approximately 17.5% of post-9/11 Veterans in VA treatment were diagnosed with back disorders and 17.0% were diagnosed with joint conditions,[4] higher rates than in comparable U.S. population cohorts.[5] Back pain, followed by neck or joint pain, is the most common cause of chronic non-cancer pain in Veterans.[6]

To decrease morbidity and mortality, a growing body of research and expert consensus support a multi-modal pain treatment strategy.[7,8] In this bio-psycho-socially-oriented model, evidence-based non-pharmacologic treatment modalities are incorporated alongside pharmacologic treatment.[9] Multiple studies have demonstrated the effectiveness of non-pharmacological pain management in improving chronic pain outcomes, including, for example, physical therapy,[10-12] cognitive behavioral therapy,[13,14] yoga,[15,16] and mindfulness based stress-reduction,[17-19] and therefore guidelines now stress the importance of a multi-modal approach.[7,20] In part to reduce prescribing of risky opioids, the availability of such multi-modal therapy at VA facilities was mandated by the 2013 Opioid Safety Initiative.[21]

<u>Veterans with MSD Are at High Risk for Substance Misuse and Need Early Intervention.</u> Veterans[22] and other people[23] with painful MSD are at high risk for developing alcohol and other substance use disorders.[24,25] Iatrogenic factors have contributed to the risk for substance use among Veterans. The opioids prescribed to treat painful MSD carry the potential for aberrant use and eventually misuse. A remarkably high proportion, 64%, of post-9/11 Veterans with *chronic* non-cancer pain have been prescribed opioids,[6] and Veterans prescribed opioids have worse outcomes than those not prescribed opioids.[26] The base rate of substance use disorders in post-9/11 cohorts is high,[27-30] and baseline substance use is a risk factor for going on to use more substances. The causality is bidirectional, in that substance use disorders predispose people to incurring injuries,[31] and are overrepresented in Veterans with pain-related comorbidities[27,32,33]

Early intervention is needed for Veterans who have chronic pain and are at risk for substance misuse or are already engaging in it. Individuals with chronic pain and SUD have worse pain-related outcomes[34] and worse addiction-related outcomes,[35] than those without comorbid pain, supporting the need to intervene early to prevent this comorbidity. Restrictions on opioid prescribing may come too late to alter the neurobiological changes associated with long-term opioid treatment for chronic pain.[36-38] These neuroplastic changes endure long after opioid treatment is withdrawn and are thought to play a key role in facilitation of transition to chronic pain. Early engagement of Veterans with chronic pain into multi-modal non-pharmacological treatments has the potential to arrest the development of risky or disordered substance use and help those already misusing substances to reduce or stop this problem behavior. Furthermore, since substance use is strongly associated with treatment non-compliance in numerous settings, early interventions that reduce risky substance use have the potential to improve pain treatment outcomes by increasing Veterans' pain treatment adherence. In this proposal, although measured separately from non-pharmacological pain treatments, substance use treatment is facilitated because it is a component of pain treatment.

2.2 Study Rationale

Compensation Examinations as a Unique Opportunity to Engage Veterans in Multi-modal Pain Care.

As of 2015, there were 971,117 post-9/11 Veterans already receiving service-connected compensation. Many of these Veterans interact with service-connection examiners at VA facilities, but they interact as claimants, not as patients. When Veterans end their military service, and begin the transition to civilian life, they are encouraged to file claims for physical or psychological conditions that may be related to their military service. Veterans are encouraged to file claims during demobilization, at Veterans' resource fairs to publicize services available to Veterans, and at Veterans Service Organizations that offer assistance with the claims process.[39] The claim is processed at the VA but does not involve clinical care.

Many of these claims are for MSD. As of 2015, there were 559,999 post-9/11 Veterans being compensated for back or neck conditions, and 596,250 for limitation of flexion in joints (Veterans often have more than one involved body part).[40] In 2015 alone, 313,052 new Veterans began receiving disability compensation, of whom approximately 31% were under age 35.

Examinations to determine Veterans' compensation are important because: (1) they are often conducted when Veterans are in some degree of pain or crisis associated with their disorder; (2) significant financial remuneration is at stake; and (3) Veterans judged to have a service-connected condition will receive *priority* care at the VA for it, typically for life. The compensation examiner has a responsibility to the agency that decides claims, the Veterans Benefits Administration (VBA), to obtain information so the claim can be adjudicated. Therefore, as in forensic evaluations, compensation examiners are taught to tell Veterans that the purpose of the examination is to evaluate the disability claim and not to provide treatment. Although the examiner's role might be complicated by him/her making a treatment recommendation, having another clinician explain available treatments is not. The failure to offer treatment can be alienating.[41]

Considerable public pressure has developed to improve the process of evaluating compensation claims such that this process includes approaches to engage Veterans in treatment. In testimony to the House Committee on Veterans Affairs, Linda Bilmes called for early intervention approaches that interface with the compensation examination process for returning post-9/11 Veterans: "VBA should shift its focus away from claims processing and onto rehabilitating and reintegration of Veterans."[42] Congressional hearings in June 2011 addressed "Bridging the Gap Between Care and Compensation for Veterans,"[43] the very topic of this proposal. One of the witnesses cited our group's editorial advocating engagement of Veterans in treatment when they apply for service-connection.[44]

Motivational Interviewing to Engage Veterans with MSD in Non-Pharmacological Pain Treatment.

Motivational interviewing,[45] a person-centered, brief psychotherapeutic approach, helps people resolve ambivalence toward positive behavioral change and strengthen their commitment to it.[46] Multiple meta-analyses have shown that MI improves treatment outcomes across a variety of behavioral domains in both medical and non-medical settings, including for substance use and treatment engagement.[47-49] MI can be

delivered in person or by telephone. Telephone-based MI has been used successfully to address substance use and other risky behaviors in a variety of populations.[50-56] It has been shown to significantly increase initiation and retention of post 9/11 veterans in both VA and non-VA mental health treatment, with a secondary effect of significantly and durably decreasing their marijuana use.[57]

Notably, MI has been found to effectively improve chronic pain treatment engagement and outcomes, especially when more than one MI session is employed.[58,59] Specifically, Habib et al[59] found that a 2-session assessment and feedback intervention based on MI, in comparison to a standard 2-session assessment and educational control interview, significantly improved the rates in which patients with chronic pain attended a series of pain management workshops. Similarly, Friedrich et al[58] showed that patients with chronic low back pain attended more physical therapy sessions and had reduced disability and pain levels when the physical therapists had been trained to use strategies consistent with MI during the patients' visits. MI is well-aligned with expert recommendations for patient-centeredness and shared decision-making in chronic pain management.[60-63] Furthermore, the VHA National Center for Health Promotion and Disease Prevention has endorsed the use of MI "to elicit and increase Veterans' own intrinsic motivation to participate in healthcare decisions and change health behaviors that are key to improving health and maintaining their well-being."[64] We propose to use MI to engage post-9/11 Veterans with MSD in multi-modal non-pharmacological pain management treatments. A recent meta-analysis of MI for chronic pain management concluded that MI is a promising approach for promoting engagement in treatments for chronic pain conditions and underscored the need for well-designed randomized controlled trials to determine the effectiveness of MI within musculoskeletal health.[65]

<u>MI-based SBIRT for Pain Management to Engage Compensation-Seeking Veterans with Chronic Pain</u>.

SBIRT is an approach to identify and briefly intervene with patients with risky substance use in settings not typically associated with addiction treatment.[66,67] The Brief Intervention in SBIRT usually is based on MI. SBIRT is efficacious for reducing unhealthy alcohol[68,69] and tobacco use,[70-72] although less well established for decreasing illicit drug use[73,74] or improving drinking outcomes for people with severe alcohol dependence.[75,76] According to our pilot data, most Veterans meeting criteria for the proposed study are likely to have episodic risky drinking rather than drug use and are not likely to have alcohol dependence (see Preliminary Studies section).

Our group developed SBIRT for Pain Management (SBIRT-PM) to promote engagement in multi-modal non-pharmacological pain management among compensation-seeking Veterans with chronic pain. In SBIRT-PM, a clinician meets with the Veteran after the compensation examination to address the presenting MSD complaint. A clinician rather than the compensation examiner delivers SBIRT-PM to allow the Veteran to engage in a confidential discussion without concern about how it will impact the compensation claim. The clinician addresses Veterans' motivation for multi-modal pain care, and explains how pain can be managed using a variety of non-pharmacological pain management services. The clinician spells out how those services can be accessed at VA.

Using permissive language about how pain is commonly self-medicated with substances, the clinician transitions to inquiries about use of prescription and non-prescription substances. The clinician then attempts to motivate Veterans to change their behavior if they are misusing substances. Thus, SBIRT-PM addresses the Veteran's presenting pain complaint first and nascent substance use subsequently.

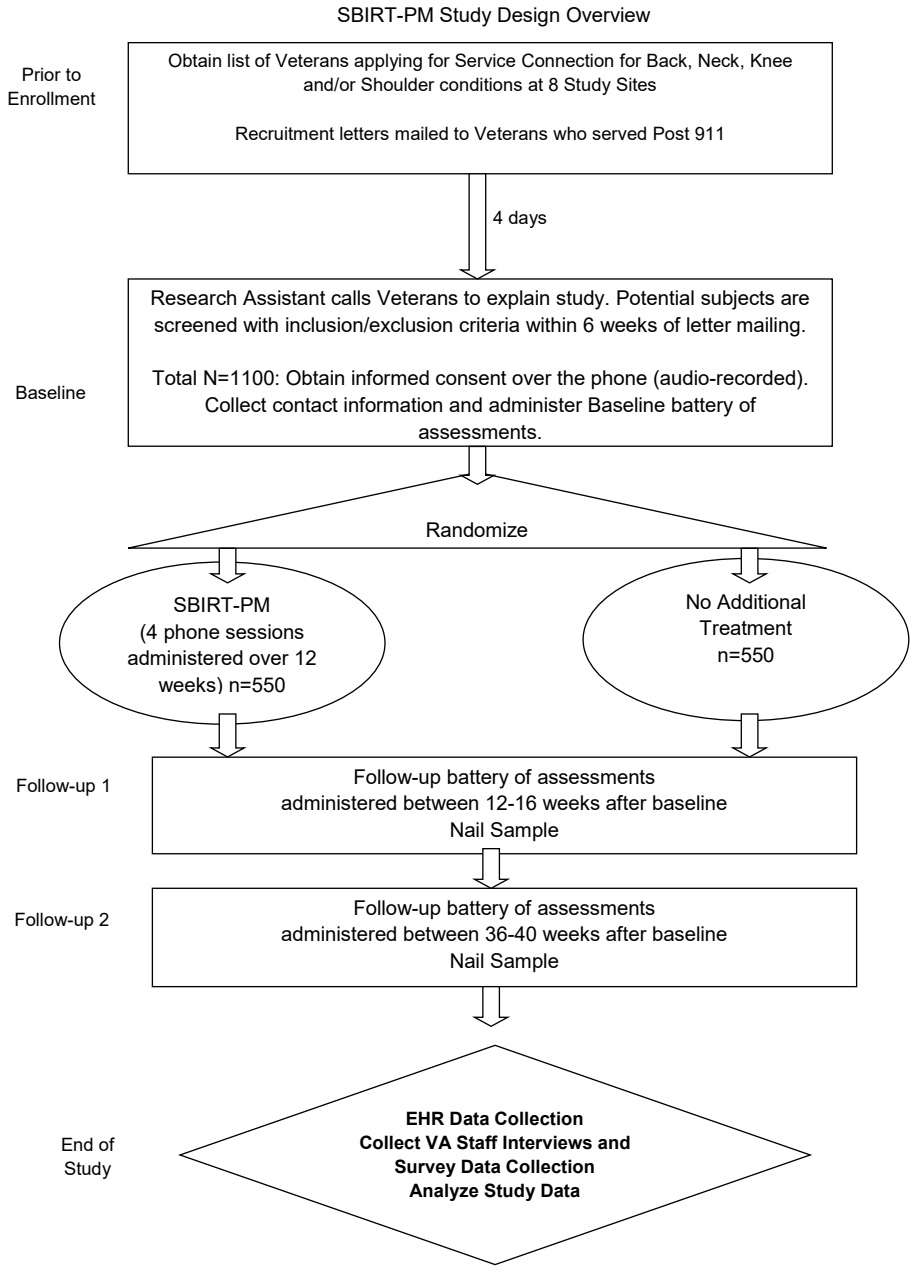
A Veterans Integrated Service Network Hub-and-Spoke Model of SBIRT-PM Delivery. The VA often employs the hub-and-spoke model to manage care across a geographically-dispersed healthcare system. The hub-and-spoke model allows for expertise concentrated in specific geographic areas to be available throughout the system. The Veterans Health Administration is divided into 18 geographical regions across the United States called Veterans Integrated Service Networks (VISN). VISNs are organized as hub-and-spoke networks in which a central administration oversees healthcare policy and service delivery of all medical centers in the designated region.[77] VISN 1 consists of eight VA medical centers and 50 outpatient clinics throughout the six New England states.

We will adopt a VISN1-wide hub-and-spoke network implementation system in which VA Connecticut Healthcare System will serve as the hub for SBIRT-PM delivery in all eight VISN1 medical centers. The hub will be the site for screening and identifying individuals appropriate for SBIRT-PM, delivering the intervention via telephone to Veterans throughout New England, and referring Veterans to site personnel who make pain management service referrals. This approach has the advantage of fitting the way in which many other clinical interventions and areas of expertise are delivered within VA. One widely used example of a hub-and-spoke model in VHA is SCAN-ECHO (Specialty Care Access Networks-Extension for Community Healthcare Outcomes). In these programs, "hubs" with experts in a particular area arrange teleconferences, trainings, and case consultation for providers in "spokes" or satellite sites. VA Connecticut is the site for a SCAN-ECHO program for pain management, and this model appears to be effective. Suggestive evidence of its effectiveness is that providers who participate in the pain SCAN-ECHO program have been significantly more likely to use physical medicine, anti-depressants, and anti-convulsant treatments, but not opioids.[78] Other examples are the VA Epilepsy Centers of Excellence to assure increased access to high quality of care for Veterans with epilepsy.[79] A hub and spoke model has the advantage of being more cost-effective compared to no network from a hospital[80] and societal perspective.[81] Hub and spoke systems allow for full-time personnel to specialize in the intervention and serve multiple sites, rather than requiring training of larger numbers of personnel at many sites.

The theoretical framework for implementation of SBIRT-PM in a hub-and-spoke model is Relational Coordination.[82] Relational Coordination refers to the quality of communication and collaboration across sites and is predictive of a team's or organization's ability to provide high quality care.[83-85] Hub-and-spoke networks function through collaborative relationships between individuals working across sites.[86] Information must flow effectively between members of the hub-and-spoke sites for care to be timely, coordinated and appropriate for the patient. In this study, we will first explore how relationships among clinical and administrative staff involved in pain care are coordinated at the sites during baseline semi-structured interviews early in the UG3

phase. Informed by what stakeholders tell us, we will then work to build Relational Coordination within our hub-and-spoke network to deliver SBIRT-PM.
Within the VA, there are financial incentives for VISN-wide initiatives, such as the one proposed, that bring Veterans into VA care. The formula for funding each VISN is essentially a capitated model of payment per Veteran, called the Veterans Equitable Resource Allocation (VERA). Each additional patient in the New England VISN generates a mean of $6500[87] (the median is considerably lower) and Veterans whose conditions are judged to be connected to their military service are, understandably, the highest priority Veterans for VA facilities to enroll. The VA as an organization depends on enrolling new Veterans as those from prior wars die or move to other regions. Beyond having the potential to improve care for Veterans applying for compensation for MSD-related claims, to the extent SBIRT-PM results in new Veteran enrollment, it could increase revenue into VISN1 and its medical centers. Therefore, our proposal includes a budget impact analysis, with the prosaic but crucial information as to how SBIRT-PM impacts the VISN bottom line. We will determine the cost and cost-effectiveness of SBIRT-PM because these data provide evidence for SBIRT-PM's value.

3. STUDY DESIGN



We will conduct a pragmatic two-arm, parallel groups 36-week multi-site randomized controlled single blind trial of SBIRT-PM. Drawing from VISN1 medical centers, we will randomize 1100 post-911 era Veterans applying for MSD-related compensation to either: 1) SBIRT-PM, a single phone-delivered session followed by up to three calls in a 12-week period and an additional call in the 12-32-week period; or 2) usual care (UC). Primary outcomes will be change in pain severity (BPI Composite severity) and change in the number of substances categorized as requiring intervention (ASSIST). The two primary outcomes will be measured by self-report at 12- and 36- week follow-ups. The self-report BPI and ASSIST measures will be completed with the Research Assistant by

telephone with the patient's responses entered directly into REDCap. The Research Assistant conducting all study assessments will be blinded. Secondary outcomes will include non-pharmacological pain management service utilization, pain interference with life activities (BPI), overall pain (PEG), overall health (EQ-5D-5L), use severity for individual substances generated by the ASSIST, and toxicology results for individual substances. The trial will include cost-effectiveness and budget impact analyses.

Study Settings.
The study will occur within the eight VISN1 VA medical centers (VAMC) located across six New England States. Each site provides MSD-related compensation examinations, addiction/mental health treatment, and a variety of non-pharmacological pain treatments.

The medical centers are:

1. Bedford VAMC
2. Boston Healthcare System
3. Central Western Massachusetts
4. Connecticut Healthcare System
5. Maine Healthcare System
6. Manchester VAMC
7. Providence VAMC
8. White River Junction VA

Feasibility of Recruiting a Sufficient Number of Veterans Who Meet Inclusion/Exclusion Criteria:
As noted in the completed SBIRT-PM RCT, in only 21 months of recruiting, 1017 examinations (for 1014 unique Veterans) were scheduled for service-connection examinations for back, neck, knee, or shoulder. Over the 32 months of recruitment for the proposed study, this would come to 1448 potentially eligible Veterans at VA Connecticut. To extrapolate from these values to the number of eligible participants we could expect at each of the other seven sites within VISN 1, we used VBA reports of new service-connection examinations requested at each of the other sites for back/neck/knee/shoulder. We then assumed the same proportion at each site would be eligible as were at the Connecticut site.

At VA Connecticut, 257/1014 Veterans met eligibility criteria and enrolled (a 24.3% enrollment rate). The proposed study is likely to enroll at least as high a percentage, and probably higher because: (1) enrollment by phone asks less of Veterans than enrollment in person required in the prior study; and (2) there are fewer inclusion/exclusion criteria in the proposed study. Conservatively assuming the 18% enrollment rate in the UG3 pilot (with only one call to many participants) yields 1862 exceeding the study's randomization goal of 1100. The large sample allows for study completion should recruitment lag at one or more sites.

The large numbers of readily recruitable Veterans in a single VISN speaks to how many Veteran are at risk and engageable at their service-connection examinations.

VISN 1 VA Medical Center	Projected Number of Post-9/11 Veterans Scheduled for MSD Service-Connection Examination over 32 Months of Study
VA Boston	2478
VA Connecticut	1448
Providence, RI	1584
Manchester, NH	1275
Togus, ME	1493
Bedford, MA	744
White River Junction, VT	677
VA Central Western Massachusetts HCS	650
Total	**10349**

Sources of Materials

Veterans sources of materials:
Information to be collected includes:

1. Veteran questionnaire responses entered into VA REDCap
2. Nail clipping toxicology tests
3. Audio recorded SBIRT-PM sessions
4. Information from the electronic health record (EHR), including the record of the Compensation examinations and service connection determination
5. Service use data from central VA databases

VA Staff sources of materials:
Information to be collected includes:

1. Responses to Relational Coordination Survey
2. Digital recordings of interviews and transcriptions

Assessment Procedures.
A research assistant, blind to study condition, will conduct baseline, 12- and 36-week participant assessments by telephone. Veterans will be instructed during the assessments not to tell the research assistant if they are receiving study counseling. To determine if the blind was maintained, the research assistant will be asked in what condition each Veteran was assigned. In the initial RCT of SBIRT-PM reported in the Preliminary Studies, the accuracy of research assistants' guesses about treatment condition assignment were almost exactly at chance (52%). We will abstract data from the VA electronic health record (EHR) when possible.

Procedures to Collect Self-Report Data from Veteran Participants.
The self-reported assessment will be conducted by phone. Baseline assessment will be conducted as soon as possible after enrollment, and follow-up phone assessments will be conducted approximately 12 and 36 weeks after randomization. Participants will receive a reminder call or text/email message prior to study appointments (e.g., "your follow-up phone interview with our research study is Monday, December 11th at 1:30. Please call [Name] at xxx-xxx-xxxx if you need to reschedule"). If a participant misses a scheduled appointment, the research assistant will call to reschedule. Participants will be asked at the beginning of enrollment for the names and telephone numbers of three

people who can find them if the research assistant has difficulty reaching them. These people will be contacted if the research team is unable to reach the Veteran within a three-week period.

Procedures to Collect Self-Report Data from VA Staff Participants

Each Site-PI will identify a list of 7-10 stakeholders (providers in primary care clinics, pain service clinics, administration, and Compensation & Pension clinics) at their site. At the end of the study (after recruitment and follow-up appointments are complete), our qualitative expert and her team will contact stakeholders by email, inviting them to participate in a semi-structured interview designed to better understand how pain services are conducted at their site and how staff at each site communicate with other clinics regarding Veteran referrals for pain services. The qualitative expert and her team will place a follow-up phone call to stakeholders to schedule an interview. Interviews will last approximately 30 minutes, and will utilize a semi-structured interview guide. Interview responses will be audio-recorded and professionally transcribed by a VA approved transcription service for later qualitative analysis.

Stakeholders will also be invited via email to complete a Relational Coordination survey, administered through VA REDCap. Survey responses will be collected confidentially and stored in VA REDCap in the secure VA environment.

Procedures to Collect Data from the VA Electronic Health Record.

VHA databases in the Corporate Data Warehouse hold patient demographics, diagnoses, and encounter information from all Veterans who have received services from anywhere in VHA. Veterans who are scheduled for a service-connection examination (all study participants) have a medical record with VHA. The encounters indicate a provider, service provider, diagnoses addressed, and clinic in which services were delivered (e.g. mental health, substance use, primary care, pain clinic). The diagnosis and service-use data are not comprehensive for Veterans who have not been receiving their care at VA, but positive findings such as treatment encounters and diagnoses reflect clinical care/evaluations and their charting by providers.

Costs Estimation Procedures.

We will use the customized Resource Allocation Worksheet to estimate the costs of delivering SBIRT-PM from the perspective of the providers (i.e., both the VISN and hospital). Cost estimation for VA services used by Veterans during the 36-week study period will be assessed using national VA administrative databases. Data on service use at the individual patient level will come from the VA National Patient Care Database (NPCD), which includes information on all inpatient and outpatient encounters at VA facilities. Costs for these services will be computed using the VA Average Cost Database, developed by the Health Economics Resource Center (HERC). The Average Cost Database assigns an average cost to each inpatient admission and outpatient visit in VA. Costs are based on Current Procedure Terminology (CPT) codes and can be linked to unique records in the NPCD.

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which includes information on all inpatient and outpatient encounters at VA facilities. Costs for these services will be computed using the VA Average Cost Database, developed by the Health Economics Resource Center (HERC). The Average Cost Database assigns an average cost to each inpatient admission and outpatient visit in VA. Costs are based on Current Procedure Terminology (CPT) codes and can be linked to unique records in the NPCD. Costs incurred by VA for community care will be obtained from databases tracking payments to community providers.

Procedures to develop a new natural language processing (NLP) algorithm that identifies use of non-pharmacological pain management services

To comprehensively identify pain-related treatment delivered to study participants, we will validate and extend existing natural language search algorithms, using previously-described procedures, to identify current use of a comprehensive set of pain treatments including those *not covered by the existing algorithms*. Those modalities will be drawn from a review of modalities used by Veterans for pain treatment and those offered in VISN 1. Algorithm development will be informed by our prior experience with this study design. We will design algorithms to maximize positive predictive value (at the expense of sensitivity) to avoid the risk of including false positives that are not randomly distributed (e.g., refused treatment referrals). The NLP extraction target will be current use of the modality. Particular attention will be paid to excluding pain discussions that do not represent treatment because they were obtained in the course of routine medical history reviews. Algorithm development involves extracting relevant snippets that mention a particular pain treatment, establishing a valid classification system for current use of that pain treatment, and optimizing the machine learning algorithm to identify current use of that treatment.

Extracting relevant snippets: In brief, terms related to each of the pain treatments (i.e. therapy keywords) will be generated by the investigative team. For example, for physical therapy, terms might include “physical therapy,” “PT,” or “physical therapist.” A simple algorithm will identify these terms, along with the 10 preceding and 10 following words. By our observation, a 20-word window is sufficient to capture most of the relevant context, and also allows for fast review of multiple records. The algorithm will be modified using Boolean terms (e.g. physical NOT physical exam). We will refine the search terms and extract 20+ word snippets using the Voogo clinical data search engine.

Establishing a valid classification system for use of a pain treatment modality: The investigators will develop annotation guidelines for classifying snippets as representing current service use (e.g. of physical therapy services as no/yes/probably). One challenge is that the documentation of temporal information varies in specificity. We will classify the temporal information into several categories based on the onset and duration attributes. For instance, usage with a non-specific past start and end time (e.g. “patient used physical therapy before”) will be considered to be past usage, usage with no specific past start but no end time (e.g. “patient has been going to a physical therapist”) will be considered current for the time of documentation, usage with specific start and end time will be considered current for the time it specified, etc. The annotation guidelines will be revised and then tested on 100 snippet samples until a kappa of 0.75 is reached between the two experts.

Optimizing the machine learning algorithm to identify use of a pain treatment: We will then randomly select 500 text snippets containing terms per type of pain therapy from all retrieved notes from primary care and perform human review based on the annotation guideline described above. Annotation work will be carried out using the Visual Tagging Tool (VTT). This set of annotates data will be added to our existing set of annotated data (n=3000) and serve as the new gold/reference standard for machine learning and training. We will apply a machine learning algorithm, Support Vector Machine (SVM), to identify current use of pain therapy, optimizing for highest positive predictive values (PPV). Informed by our prior experience, we will use therapy keywords, n gram (n consecutive words), note type, and temporal information as features in the classification of current use. Temporal information will be extracted using a prior method developed and tested by Dr. Zeng.[88]

To assess the NLP performance, we will perform 10-fold cross validation, which partitions the entire annotated sample into 10 random sets with equal size, uses 9 sets for training and 1 for testing, and repeats 10 times. Our target PPV is >=90%, which is very likely to be reachable because: 1) the specificity of the test has been set high (at the cost of sensitivity); 2) the usage level (prevalence) of the primary non-pharmacologic modalities for chronic pain treatment is high which increases PPV; 3) we achieved 89% PPV in our work on a small set of modalities. We will apply machine learning methods we trained using previously acquired annotated data such as Support Vector Machine and Random Forest, and will use an ensemble learning step called Stacking,[89] in which a learning algorithm combines the results of several other learning algorithms, if the separate programs' performance fails to reach the target positive predictive value. In the unlikely event that the PPV is not reached for a particular CIH modality, that modality's assessment will be conducted by the other two available methods (self-report and EHR codes).

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

For this pragmatic clinical trial, the study inclusion and exclusion criteria are broad. There are no specific evaluations of capacity to consent or complete study procedures.

Participants must meet all the inclusion criteria to participate in this study. Consistent with the guidelines for pragmatic trials, we have taken a broad perspective to include all participants who have MSD-related conditions with moderately severe pain, regardless of the type of MSD, their anticipated responsiveness to SBIRT-PM, or psychiatric, substance use, or medical comorbidities or past compliance. Because SBIRT-PM targets pain, and is telephone-based, at baseline participants must self-report moderate pain severity and have access to a telephone to test the effectiveness of the SBIRT-PM in this clinical trial. The other targeted outcome, substance use, is not an inclusion criterion. But rates of risky use in the completed RCT were high enough for an adequately-powered study without requiring baseline use as an inclusion criterion.

Candidates meeting any of the exclusion criteria at baseline will be excluded from study participation. We are excluding people who are already connected to three or more VA nonpharmacological pain to minimize a ceiling effect, i.e., such participants have a lower likelihood of needing a referral.

4.1 Inclusion Criteria

1. post-9/11 Veteran applying for MSD-related compensation (specified as back, neck, shoulder, or knee pain), as ascertained from filed claim,

2. reports a score of ≥4 (threshold for moderately severe pain) on the BPI's Pain Severity subscale (average of four pain intensity items);

3. availability of a landline or cellular telephone for SBIRT-PM.

4.2 Exclusion Criteria

1. reports inability to participate during the study enrollment call;

2. received three or more non-pharmacological pain treatment modalities within the last 12 weeks from VA (modalities are: (1) acupuncture (2) rehabilitation therapies (3) Manipulation (4) Massage (5) Yoga (6) Tai Chi/Qigong (7) exercise (8) Biofeedback (9) Hypnosis/Hypnotherapy (10) Guided Imagery (11) Meditation (12) Psychotherapy/Counseling (13)Reiki (14) teaching about coping with pain (15) other treatment for pain);

3. participation in another PMC3 study as evidenced by a research protocol alert for that study at the time the study invitation letter is mailed.

4.3 Study Enrollment Procedures

Human Subjects Involvement. The proposed project will include two groups of human subjects, (1) Veterans and (2) VA staff (clinicians and administrators).

Screening and Recruitment for Veterans.
A waiver of Informed Consent and a waiver of HIPAA Authorization were obtained to review the Compensation and Pension Clinic's schedule to determine when a MSD examination is scheduled for a post-9/11 Veteran. The waiver allows for the collection of basic demographic information concerning Veterans screened for study participation to determine if Veterans who consent to study participation differ systematically from those who do not. The proposed study will employ recruitment procedures used in Compensation Clinic-based studies by our group. There have been no adverse events associated with these recruitment procedures.
The recruitment strategy involves first identifying Veterans scheduled for a compensation examination for a MSD by reviewing chart and Compensation Clinic information about Veterans scheduled for these evaluations. A research assistant at the hub site will exclude people whose records preclude post-9/11 military service and mail recruitment letters. These potentially eligible Veterans will be mailed a letter from the

research team explaining the basics of the study and that unless the Veteran opts out, a member of the research team will call to further explain the study. A toll-free phone number will be included in the letter that Veterans can call to opt out of receiving the phone call or to express their interest in participating. A magnet with study contact information and $1 USD will be included with the recruitment letter. All veterans who are identified as a potential participant and mailed a recruitment letter will receive the magnet and dollar regardless of whether or not they choose to enroll in the study. The magnet is a non-monetary incentive (valued at approximately $0.21) that will increase response rate, as potential participants can post the magnet in an easy to see location to remind them that the study personnel will be calling. It might also help with retention rates for enrolled participants as it can be a visual reminder of participation and the study team contact information will be readily available. The dollar is a monetary incentive designed to increase the rate at which people will take the study team call. One year into the study, we have found that we are unable to contact 45% of people who are mailed a letter after three contact attempts. Research has shown that pre-paid incentives are most effective at increasing response rate. However, the value of the incentive is nominal so as not to be coercive or to create an undue influence on people from a lower socioeconomic class.

Veterans who opt out will not receive any more study-related phone calls. A copy of the Study Information Sheet describing the study will be included with the recruitment letter.

At least four days after the recruitment letter is sent, research assistants will attempt to call Veterans up to three times to invite them to participate in the study. A four-day waiting period from the day the letter is mailed to the day of the call is sufficient to allow Veterans time to receive the letter in the mail and opt out if preferred. At that call, the research assistant will explain the study and further screen for eligibility. For eligible Veterans, the research assistant will conduct informed consent followed by baseline assessments during this phone call or subsequently. Although enrollment ideally occurs before the Compensation examination, Veterans will be allowed to enroll up to six weeks after recruitment letters are mailed. If a Veteran misplaces or has not received the Study Information Sheet, the Research Assistants will offer to mail another copy to the Veteran. The Veteran can choose to continue with the recruitment call or to wait until they receive the copy of the Information Sheet before continuing.

<u>Informed Consent and Enrollment for Veterans:</u>

Voluntary informed consent will be obtained from all Veterans prior to participation. A waiver of Documentation of Informed Consent and a waiver of HIPAA Authorization has been obtained for this study.

Participants will receive a Study Information Sheet detailing the study. In an audio-recorded telephone call, a research assistant will go over all aspects of informed consent with potential participants. At the start of the call, the research assistant will verify the identity of the participant. Veterans will be provided with information about the SBIRT-PM intervention, how long it will last, the nature of study assessments, information about the collection of biological specimens, the examination of their electronic health care and VA data, and potential risks and benefits of study participation. Veterans will be reminded that they can withdraw from the study at any

time without penalty. They will be given the opportunity to ask questions and then will be asked if they agree to participate.

Veterans who agree to participate will state so for the audio-recording. Audio-recorded consents will be stored in a restricted research investigator folder on VA Network computers behind the VHA firewall. Only research staff will have access to the recordings.

Staff obtaining verbal consent will have completed a web-based course with post-test on Human Research Protections, and all will have had specific training by the mPIs in obtaining informed consent for this project. All staff obtaining consent will be authorized to do so by the VA Central IRB.

Justification for obtaining a waiver of documentation of informed consent and waiver of HIPAA Authorization: These waivers are necessary to conduct the study. The purpose of this study is to test the usefulness of remotely delivered counseling. All counseling sessions and research assessments are conducted remotely. There is no face-to-face contact with participants and the study is considered minimal risk. It would be burdensome and impractical to have potential participants come in to the VA just to sign a study Consent Form and HIPAA authorization. This study could not practicably be conducted without the waivers due to the timing of study procedures. Baseline assessments and study counseling should occur before or within six weeks after the recruitment letter is mailed. Waiting for the Veteran to find time to come to the VA to sign a Consent Form and HIPAA Authorization or waiting for the Veteran to return a signed copy of the Consent Form and HIPAA Authorization by mail will likely push the timing of study assessments outside of this window, making a large proportion of eligible Veterans ineligible.

Randomization: The unit of randomization is participant. Participants will be randomized to SBIRT or Usual Care using a computerized urn randomization program[90] within each site to increase the likelihood of balanced allocation of participants to the two interventions on sex, race (Caucasian, African American), ethnicity (Hispanic no/yes) and self-reported illicit drug use within 90 days. The research assistant will be blind to the assigned condition. For each participant, Research Assistants will communicate data needed for the urn to the Project Director, who will randomize the participant and assign a study therapist based on location, availability and work flow.

Enrollment: Participants are considered enrolled after they complete the informed consent process and agree to study procedures.

Informed Consent and Enrollment for VA Staff:

A waiver of documentation of Informed Consent for VA Staff participants has been obtained for staff participants.

Research staff will describe the purpose of the survey and interview prior to administering these assessments. Participating VA staff members will be encouraged to ask any questions and have the option to discontinue participation without prejudice. They will be approached by people other than their direct supervisors.

After a brief reiteration of the study purpose, the interviewer will confirm consent to record the interview for transcription and analysis purposes before proceeding.

Screening for medical record review to develop the natural language processing (NLP) algorithm for pain-related treatments.
A computer algorithm will be used to identify key terms (e.g. “physical therapy” along with the 10 preceding and 10 following words: a snippet. Snippets of chart data will be identified that contain pain-related treatment keywords and surrounding text will be identified from electronic medical records from up to 10,000,000 (approximately number of Veterans with medical records). As such, although not specifically queried for PHI, a snippet might contain some PHI such as a visit date and doctor’s name. All of the work with the snippets is done in the VINCI data analysis environment behind the firewall in the VA. Access to the VA network and VINCI are password protected and only accessible at the VA or through remote access with an approved device. These snippets will be reviewed to identify approximately 700 snippets per pain treatment modality (100 for developing annotation and 600 for validating the algorithm using the developed annotation).

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

SBIRT-PM Intervention.
SBIRT-PM involves a manualized, motivational interviewing-based 4-session telephone-delivered intervention over a 12-week period to motivate Veterans to engage in multi-modal non-pharmacological pain care and, for those with co-occurring risky substance use, also change this problematic behavior. SBIRT-PM also includes coordination between the SBIRT-PM counselors and the PACT nurse case manager or primary care provider after the initial session to support these patient outcomes. SBIRT-PM will be delivered centrally from the VA Connecticut hub to the VISN1 medical centers by counselors trained in the approach. All sessions will be audio recorded for the purposes of SBIRT-PM fidelity assessment and supervision.

Initial Session.
The initial session is conducted after the compensation examination for the presenting MSD complaint. The counselor begins by explaining the separation between any service-connection claim and the counseling, as we have done in prior studies. The counselor also explains the structure (4 sessions over 12 weeks), and focus (engagement in pain management services, changing risky substance use if it exists) of SBIRT-PM and then begins the interview by asking about the Veteran’s MSD condition and experiences with pain, conveying understanding and compassion for the Veteran’s experience. Next, the counselor explains how pain can be managed using a variety of pain management services, and how these services can be accessed at VA.

The counselor explains pain management consistent with guidelines issued by the American College of Physicians,[91] calling for education, encouragement of self-management, and judicious use of non-opioid medications. The explanation is in the spirit of providing information, not an exhortation. The counselor describes how the goal of pain treatment is improving function (“helping you get back to doing things that are important to you”) and that it may take a variety of different treatments to achieve this

goal. The counselor further describes how pain is commonly associated with decreased activity, which in turn can contribute to other problems.

The counselor's explanation of the role of opioid medications paraphrases messages that primary care providers deliver to Veterans as part of Dr. Becker's safe prescribing approach.[92] The counselor explains that medications, including both opioid and non-opioid medicines, have an important place in some Veterans' pain treatment, and that Veterans benefit when pain medicines are prescribed and taken safely. The counselor reinforces the importance of taking opioid medicines as prescribed because there are risks of addiction and interactions with other substances (like alcohol). The counselor explains that judicious use of non-opioid medications improves pain treatment outcomes without these risks.

The counselor introduces the idea that non-pharmacological treatments can help manage pain, and explains what they are and how they work. These services may include: (1) treatment for the underlying ailment, (2) physical therapy (both at VA and as home exercise and stretching programs), (3) behavioral treatments like Cognitive Behavioral Therapy for chronic pain, (4) treatments for depression, PTSD, and/or other mental health problems that chronic pain may have aggravated, and (5) complementary and integrative health interventions available including chiropractor services, acupuncture and yoga.

Throughout these discussions, the counselor seeks opportunities to motivate the Veteran to engage in multi-modal pain care using a variety of MI consistent approaches. If the Veteran commits to engaging in pain management services, the counselor develops a plan with the Veteran to initiate this process. For Veterans not enrolled in VA services, the counselor explains the procedures to obtain eligibility for VA care.

- After motivating Veterans for engagement in pain management services, the counselor transitions to screening for substance use. The counselor explains that some people with chronic pain use various substances to help them cope with the pain, and obtains the Veteran's permission to discuss this. The counselor then screens for substance use. If the Veteran reports no risky substance use, the counselor summarized the session, reiterates the plan, and schedules the next session. If the Veteran reports risky substance use, the counselor asks more about it and how the use is affected by the Veteran's pain. The counselor provides feedback about the risky substance use, including evidence that people who don't misuse substances have significant reductions in their pain compared to those who continue to do so. As with efforts to address the Veteran's interest in pain management services, the counselor uses MI consistent approaches to motivate the Veteran to stop or reduce risky substance use. Some Veterans will not want to pursue abstinence and, for them, a harm reduction approach will be taken, meaning the counselor and Veteran will negotiate a plan to use less of the problematic substance per occasion, or use on fewer days, but not necessarily strive for abstinence. The counselor will develop a plan with the Veteran about how to reach a goal of abstinence or reduced or less frequent use, including options for engaging in specialty addiction treatment services available at the VA. When mental health issues further complicate the Veteran's pain management and risky substance use, the counselor will also discuss these issues with the Veteran. In fact, some Veterans may insist on PTSD (or depression) treatment instead of substance abuse

treatment, and, consistent with MI, Veterans will receive information about preferred available treatments, including if the Veteran prefers to first talk with the primary care provider about his or her addiction or mental health concerns.

Follow-up Sessions.
After the initial session, the counselor will have up to three 20-minute, mutually scheduled phone counseling sessions with the Veteran (about once per month for 12 weeks) to check on the Veteran's status in achieving the goals of the plan, and to gauge his or her continued motivation to receive pain treatment and reduce risky substance use, as indicated. An additional call during the 12-32-week period is permissible to re-motivate veterans to engage in available pain and substance use services in view of any healthcare system changes that occurred (see response to COVID-19 section below). These calls may be informed by information the counselor has obtained from the PACT providers or information in the electronic health record (e.g., seeing if a consult was placed, reviewing progress notes indicating engagement with services). Twelve weeks allows time for the Veteran to work with the counselor to resolve barriers to service engagement, consider other treatment options, and sustain motivation for and engagement in pain management and ancillary services. Moreover, meta-analyses and "dose-response" studies[93,94] have suggested the benefit of several follow-up telephone sessions.

Coordination with PACT Providers. The counselor will communicate with the PACT nurse case manager and primary care provider, or other point-of-contact about recommended pain treatment referrals primarily via the electronic health record. SBIRT-PM counselors will write progress notes that indicate the SBIRT-PM encounter and outcome of each session, including asking the provider to consider placing a consult for the Veteran's preferred services or discussing the Veteran's interest in services at the Veterans next scheduled appointment. SBIRT-PM counselors cannot place consults for services directly; only PACT providers or other licensed professionals working with the Veterans at their VAs can do so.

SBIRT-PM Clinician Supervision.
Dr. Martino will provide competency-based supervision to support the counselors' delivery of SBIRT-PM throughout the trial. This approach is consistent with the national VA Evidence-Based Practice training model,[95] which emphasizes extended post-workshop case-based supervision or consultation, including submission of audio recorded therapy sessions for treatment fidelity review, as an essential training component. Dr. Martino will meet with the counselors together on a 1-hour monthly basis to review their SBIRT-PM practice. For these supervision meetings, he will listen to and rate the counselors' SBIRT-PM fidelity for two sessions per counselor (one initial and one follow-up call) using the Independent Tape Rater Scale [96] (see 3.C.3.8.10) for the purposes of feedback and coaching during supervision. In MI clinician training research, this approach and dose of supervision has been shown to sustain proficient practice.[97]

Adaptations to intervention in response to COVID-19.

Because the intervention is delivered via telephone and involves no in-person contact, we are able to continue to deliver the intervention during the coronavirus pandemic. However, several adaptations will occur.

1. Access to in-person pain and substance use treatment is extremely limited during the pandemic, while the VA has expanded telehealth/video-based visits and treatments. Therefore, SBIRT-PM counselors will advise veterans on available telehealth/video services and online resources for pain and substance use treatment that Veterans are being referred to.
2. Counselors will make themselves as widely available as possible to accommodate tighter schedules.
3. Empathy for the Veteran's situation is a core feature of Motivational Interviewing and many Veterans' situations are dominated by COVID-19. Therefore, empathy for COVID-19 related issues that Veterans raise is being incorporated into the counseling.
4. Because of the changing availability of treatment services during the COVID-19 period, the intervention will allow for one additional counseling session per veteran to occur between weeks 12 and 32. This session will be for the purpose of re-motivating veterans to engage in available pain and substance use services in view of any healthcare system changes that occurred. The additional session maintains the integrity of our intervention in that the counselor can fully influence veteran engagement in multimodal pain treatment and addiction services as those services' availability changes.
   Counselors will determine on a case-by-case basis when to conduct this additional session based on when services become more available at each site and veteran preferences. Only one session will be permissible during this week 12-32 period, regardless of the number of sessions completed during Weeks 1-12. All participants in the SBIRT-PM condition currently are within 32 weeks post-randomization and thus eligible to receive the additional session. The additional counseling session will remain part of the protocol for the duration of the trial.

Usual Care.

A Veteran who completes a Compensation examination ordinarily has no further treatment, referral or debriefing as part of the Compensation examination. Veterans assigned to the control condition will be contacted by the Project Director and will be told they were assigned to the condition without additional study counseling. Veterans will be reminded that they should continue to pursue whatever counseling they need outside the study.

Justification for No Additional Referral Control Condition. No additional treatment is "treatment-as-usual" when a Veteran applies for service-connection. However, no treatment that a Veteran would otherwise get without participating in this study will be withheld. An active control group is important when an extensive intervention is being tested and it is important to determine if the intervention's efficacy apart from non-specific benefits from the time and effort expended by the clinician. However, the need for an active control group is less compelling when compared to a relatively brief intervention[98] and when conducting a pragmatic trial where the emphasis is testing the effectiveness of innovations that improve upon usual clinical care.[99]

5.2 Handling of Study Interventions

Study counseling sessions will be administered over the telephone in accordance with the counseling manual. After a counseling session has occurred, study counselors will place a note in the Veteran's electronic medical record indicating that a counseling session occurred and listing referrals the Veteran is interested in having placed.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

N/A. Participation in this research study does not preclude use of any medications.

5.3.2 Required Interventions

N/A.

5.3.3 Prohibited Interventions

None

5.4 SBIRT-PM Fidelity Assessment

SBIRT-PM fidelity assessment will involve tracking the number of counseling sessions conducted per participant and the adherence and competence with which counselors conduct the sessions. All SBIRT-PM sessions will be recorded and counselors will maintain contact logs indicating all contact attempts made to participants, result of each contact, and duration of each counseling session.

Adherence and Competence: We will randomly select 220 audio recorded SBIRT-PM sessions from the total number of sessions occurring in the trial (maximum = 550 initial + 1650 follow-up sessions). Therefore, at a minimum we will have a 10% sample for validating that SBIRT-PM was delivered as intended. Specifically, the Independent Tape Rater Scale (ITRS) will be used to assess the degree to which SBIRT-PM sessions were delivered with fidelity to MI (i.e., with adherence and competence). The ITRS includes items that cover therapeutic strategies that are MI consistent (e.g. reflections) or inconsistent (e.g., unsolicited advice). For this trial, we added three general items that detail the extent to which strategies for pain and substance use occurred in the sessions. For each item, raters evaluate the counselors for adherence (i.e., the extent of intervention delivery) and competence (i.e., the skill/quality of intervention delivery) along 7-point Likert scales. We will: 1) calculate mean adherence and competence scores for the two factors (fundamental and advanced MI strategies) identified in prior psychometric analyses,[96,100,101] and 2) determine if sessions achieve a criterion level for adequately performing MI, namely, at least half the MI consistent items rated average or above for both adherence and competence. In addition, we will evaluate the degree to which clinicians addressed pain and substance use during the session, based on our general items. We have documented experience training ITRS raters to perform reliable MI session process ratings in multi-site trials.[102-106]

For the data analyses, adherence to SBIRT-PM counseling will be dichotomized ("Having received counseling" Yes/No). This approach is being taken because SBIRT-PM's duration and intensity is not hypothesized to relate to outcome; a Veteran might, in a single session, take steps to engage in non-pharmacological pain treatment that require minimal follow-up. Conversely, a Veteran with more follow-up sessions might have more because the Veteran is more ambivalent about non-pharmacological pain treatments and is receiving more counseling because of more need for it. After the completion of the intent-to-treat analyses, the adherence indicator will be added to examine it as a potential mediator of response in the primary outcome analyses.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

RCT Assessments

Assessment Name/Domain	Data Source	Baseline	12-wk	36-wk
Socio-demographic Characteristics	Self-Report	x		
Psychiatric and Substance Use Diagnoses	VA EHR -structured data (e.g. clinic codes)	x		
Characteristics of Musculoskeletal Disorders	VA EHR, Service-connection exam	x		
Distance to nearest VA Facility	VA EHR		x	
Brief Pain Inventory	Self-report	x	x	x
Numeric Rating Scale	Self-report	x	x	x
Opioid Medications Dispensed in Morphine Equivalent Daily Dose	VA EHR	x	x	x
Non-opioid Medications Dispensed	VA EHR	x	x	x
Non-pharmacological Pain Management Service Use—VA services	VA EHR -structured data (e.g. clinic codes)	x	x	x
Non-pharmacological Pain Management Service Use---VA and non-VA services	VA EHR with Natural Language Processing	x	x	x
Self-reported VA and non-VA service use	Self-report	x	x	x
ASSIST	Self-report	x	x	x
Prescription Opioid Misuse	Self-report	x	x	x
Nail clippings for drug/etoh use metabolites	Biological	x	x	x
Substance Use Treatment Service Utilization – VA services	VA EHR -workload data and clinic codes	x	x	x
Self-reported VA and non-VA substance use service use	Self-report	x	x	x
PHQ-9 (depression)	Self-report	x	x	x
EQ-5D -5L	Self-report	x	x	x
PEG	Self-report	x	x	x
Motivation for engaging in pain treatment	Self-report	x	x	x

High Impact Pain Questions	Self-report	x		
Audit-C	Self-report	x		
COVID-19 questionnaire	Self-report	x	x	x

UG3 Preparation Assessments and End-of-Study Assessments

Measures Described Earlier in UG3 Stage of RCT preparation	**Data Source**	**UG3 preparation phase**	**End of Study**
Qualitative Interviews of Stakeholders	Self-report	x	x
Post-intervention Interview of SBIRT-PM-treated Veterans	Self-report	x	
Relational Coordination Survey of Key Stakeholders	Self-report	x	x
Treatment Fidelity Measure: Independent Tape Rater Scale	audio recorded SBIRT-PM session ratings		x

6.2 Description of Evaluations

6.2.1 Screening Evaluation

A waiver of HIPAA authorization and waiver of informed consent have been obtained to access lists of Veterans applying for Compensation and Pension benefits for back/neck/knee/shoulder conditions at 8 study sites. Identified individuals who are post 9-11 status will be mailed a letter explaining the study. Individuals will be eligible for enrollment for up to 6 weeks after the letter was mailed. The SBIRT-PM intervention acts by engaging Veterans in pain treatment, and Veterans who have not engaged in three or more non-pharmacological pain treatment modalities (one of the inclusion criterion) still are at the stage of care that they could benefit from the proposed counseling.

Four days after the mailing, research assistants will follow-up the recruitment letters with a telephone call to fully screen Veterans for inclusion in the study using the participant screening form. Screening forms will be saved in the research study folder on the VA secure network. The screening evaluation after the letters are mailed consist of a few questions about pain treatments received, pain severity, and availability of a phone.

Individuals who meet all inclusion/exclusion criteria and are interested in participating in the study will be consented over the phone.

Consenting Procedure

A waiver of HIPAA authorization and a Waiver of Documentation of Informed Consent have been obtained to consent participants into the study. Research Assistants will consent eligible individuals into the research study by telephone call. Research Assistants will audio record the informed consent process for individual to enroll him/her into the study. Audio files of the informed consent process will be saved in the research study folder on the VA secure network.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

The enrollment date is that day the individual has met all the screening criteria and has agreed to participate in the study by completing audio-recorded informed consent.

Baseline Assessments

Measures to Characterize the Sample.

- Socio-demographic Characteristics. A research assistant will collect self-reported socio-demographics (age, sex, race, ethnicity, marital status, education, employment status, legal status, and military history) from Veterans during baseline assessment.
- Medical Diagnoses. We will extract medical diagnoses from electronic health records and the VA Corporate Data Warehouse. We will identify psychiatric (e.g., depression, anxiety, Traumatic Brain Injuries,[107,108] and PTSD[109,110]) and substance use disorders in the EHR and VA Corporate Data Warehouse by their ICD-9 and 10 codes. We decided against more direct measures of psychiatric conditions (e.g. the PTSD Checklist) to minimize participant burden and reactivity. To increase the sensitivity of our detection of psychiatric conditions, we will extract the service-connection claims data from the Veterans Benefits Management System for study participants at the end of their study participation. New recipients of service-connection receive it for an average of 5.25 distinct claims,[40] and many Veterans file both MSD and claims for mental conditions at the same time. This will identify Veterans with psychiatric disorders who were diagnosed during their service-connection examinations but do not have a diagnosis in VA treatment records because they were not treated for their mental health condition.
- Characteristics of Musculoskeletal Disorders. We will determine the diagnostic group of MSD assigned to participants in the EHR by using ICD-9 or 10 codes. Major groups are back pain, neck pain, and osteoarthritis. Other categories will be combined as suggested by their frequency and co-occurrence with other MSD. These include non-traumatic joint disorders, osteoporosis, sprain and strain, traumatic joint disorder, spinal cord injury, fibromyalgia, rheumatoid arthritis, temporal mandibular disorder, lupus, gout, and MSD multimorbidity (more than one MSD diagnosed). The broad MSD groups will be considered as potential moderators of treatment effect in the analyses. In addition, compensation examiners complete a detailed, structured form, the Disability Benefits Questionnaire (DBQ), for each Veteran they evaluate. From these forms, we will extract structured notations of the examination findings. Finally, we will obtain the final percentage service-connection awarded from the Veterans Benefits Administration System (VBMS) after the determination, and delineate service-connected conditions.

Pain Measures:

- Brief Pain Inventory (BPI). The Brief Pain Inventory[111] (BPI) is a validated instrument to assess chronic non-cancer pain that yields two subscales. One measures pain severity (4 items on a 0-10 scale) and the other assesses pain interference with life activities (7 items on a 0-10 scale), both using a 24-hour recall period. BPI pain

severity will serve as our primary pain outcome for the trial; pain interference will serve as a secondary outcome. The BPI is a reliable measure and responsive to change.[112] The BPI is endorsed by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group[113] as a preferred measure of pain-related functioning. IMMPACT recommendations have specified score changes that would represent a minimally clinically important difference (i.e., 30% reduction in pain severity and 1-point reduction in pain interference), which will be used in our cost analyses.[114]

- Numeric Rating Scale (NRS). The NRS[115] is an 11-point (0 = no pain, to 10 = worst pain imaginable) scale for current pain. It is the only pain measure collected at point-of-care for every Veteran as part of the vital signs assessment in Primary Care and entered into the EHR. The NRS has several shortcomings: a) Veterans may seek services when their pain levels are high, thereby masking longitudinal improvements in pain intensity; b) point-of-care contacts vary substantially among Veterans in Primary Care, rendering systematic analysis of changes in pain symptoms difficult to ascertain in a clinical trial; and c) point-of-care NRS significantly underestimates pain intensity compared to same-day paper-and-pencil NRS assessments.[116] Balancing the ubiquitous use of NRS with its limitations, we will examine EHR-abstracted NRS ratings for participants as a secondary outcome.
- PEG[117]. The PEG is a 3-item scale assessing pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G) during the past week. It has good reliability, constructive validity, and sensitivity to change and has been required by the NIH-DoD-VA Pain Management Collaboratory Coordinating Center as a common measure across funded protocols.
- High Impact Pain Questions. Three questions to determine the long-term impact of pain are being asked: "In the past 3 months, how often did you have pain?"; "Over the past 3 months, how often did pain limit your life or work activities"; "Are you not working or unable to work due to pain or a pain condition?
  Answer choices consist of "never", "some days", "most days" or "every day" for the first two questions and yes/no for the third question.

Pain Treatment Services Received:

- Opioid Medications Dispensed. We will extract dispensed opioid medications and dosages from the patient's electronic medical record and convert them to morphine equivalent daily dose using the procedures from a published algorithm[118] as adopted and operationalized by the PMC3 Phenotypes and Outcomes workgroup.
  Medications will be classified as opioids used to pain as follows:
  (1) All non-IV fills of:
    a) Codeine
    b) Fentanyl
    c) Hydrocodone
    d) Hydromorphone
    e) Morphine
    f) Oxycodone
    g) Oxymorphone
    h) Tramadol

(2) All non-IV, pill/tablet pills of:
a) Methadone
(3) All transdermal or buccal fills of
a) Buprenorphine

MEDD is calculated by assuming prescriptions were taken as directed. Total morphine equivalents are calculated by multiplying the quantity of each prescription by the strength of the prescription (milligram of opioid per unit dispensed). Standard conversion factors on the CDC website will be used to estimate the number of milligrams of morphine equivalents dispensed. Average daily morphine equivalent dose will be calculated by dividing total milligrams of morphine equivalents by days supplied. For prescriptions that apn a particular month, only dates during that month will be included.

The PMC3 Collaboratory recommends the following be collected, and we will collect and analyze them per their recommendations:

a. Number of opioids supplied
b. Days supplied
c. a/b x conversion factor = milligrams morphine equivalent daily dose (MEDD)
d. Mg MEDD at enrollment
e. Mg MEDD monthly during enrollment and at study completion.

- Non-opioid Medications Dispensed. We will extract dispensed non-opioid pain-related medications from the medical record. These medications will include topical analgesics, non-steroidal anti-inflammatory drugs, anticonvulsants, and antidepressants (specifically, selective serotonin and norepinephrine reuptake inhibitors and tricyclic antidepressants). The presence or absence of medications in each class will be the dependent measure.
- Non-pharmacological Pain Management Service Utilization-VA Records. Dr. Goulet and the PRIME Center have an algorithm for identifying visits from the EHR involving non-pharmacological management using workload information entered at clinic visits (e.g. diagnosis treated, procedure performed) and the type of clinic providing the treatment.
- Natural Language Processing-identified Non-Pharmacological Pain Management Service Utilization-VA and non-VA service use. This identifies dates at which the Veteran has reported “current use” of specific pain management modalities.
- Self-Reported Use of Pain Treatment Services. The PMC3’s phenotype and outcomes workgroup developed the “Use of nonpharmacological and self-care approaches” questionnaire to collect information about patients’ use of 13 different pain treatments, including Acupuncture, Rehabilitation Therapies, Manipulation, Massage, Yoga, Tai Chi/Qigong, Exercise, Biofeedback, Hypnosis/Hypnotherapy, Guided Imagery, Meditation, Psychotherapy/Counseling. In addition to asking about whether each treatment category was used, the instrument also includes questions about the most important reason for use, whether the treatment was received from a practitioner, the type of setting of use, how the service was paid for, how often it was used, and how effective it was in relieving pain. The instrument was modified for this study to collect information over the past 3 months (instead of past year), and to include several additional categories: Reiki, Pain School, Pain Clinic, primary care services, emergency/urgent care services, opiate and non-opiate medications.

Substance Use Measures:

- ASSIST. Substance use will be measured over the last 3 months using Version 3.1 of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). After a screening question focusing on substances *ever* used, the ASSIST consists of seven questions about use of and consequences of use of each of ten classes of substances over the preceding three months (including nicotine). Scores are generated for each substance that are mapped to a three-point ordinal scale of severity.[119] As outlined in the World Health Organization's Manual describing the use of the ASSIST to guide treatment recommendations, the ASSIST ratings are scaled to represent no need for treatment, need for a brief intervention, and need for an intensive intervention. An advantage of the ASSIST is that these categories represent what clinicians consider a clinically important difference, in that they guide treatment recommendations. The items in the ASSIST have been shown to have good to excellent reliability for the substances assayed. The reliability of the individual ASSIST items,[120] and the ASSIST's concurrent validity compared to other more detailed assessments of substance use severity[121] have justified its adoption by the World Health Organization.[122] We will obtain additional specifiers for substances requiring further characterization: a specifier about use of vaping for tobacco products, a specification as to whether the Veteran is using legal or prescribed cannabis and specification about use of prescribed amphetamine.
- Prescription Opioid Misuse. Two questions,[123] adapted from the CIDI[124] for use in a NIDA Clinical Trials Network study,[125] will be used to describe misuse of prescribed opioid medications: *"How often have you taken your pain medications in larger amounts than prescribed or for a longer period than prescribed?" and "How often have you used your pain medicines to get high, to relax, or to make you feel more alert?"* The questions are asked about the preceding 4 weeks, with follow-up questions to clarify that the question refers to opioids only.
- Nail Collection and Measurement. Nail clippings will be assayed for metabolites of alcohol (ethyl glucuronide i.e. ETG), cannabinoids (carboxy-THC, native-THC), opioids (6-MAM, codeine, hydrocodone, hydromorphone, morphine, oxymorphone, oxycodone), Amphetamines (amphetamine, MDA, MDEA, MDMA, methamphetamine), Cocaine (benzoylecgonine, cocaethylene, cocaine, norcocaine) and Phencyclidine (PCP). The tests are highly specific. Samples are analyzed using an immunoassay technique (ELISA) and non-negative specimens are subjected to a gold standard confirmation technique (GCMS or other method, depending on drug class). Nail, like hair, traps biomarkers in keratin but has higher concentrations of neutral and acidic biomarkers because it has thicker keratin. In a study of hair and nails collected from the same people, the rate of Carboxy-THC (an acidic biomarker for cannabis) positives for cannabinoid at the SAMHSA-recommended cutoff was 46.7% for hair and 53.3% for fingernails and mean concentrations of the metabolite were five-fold higher in nails than in hair.[126] In a study in the journal *Addiction* of 606 college students,[127] nail ETG at the 8 pg/mg threshold proposed for this study detected high-risk drinking with a sensitivity of 1.0 and a specificity of .63. Receiver operating characteristic curves were significantly higher for ETG concentration in fingernails than in hair for detecting risky drinking.

The biomarkers are incorporated throughout the nail plate from base to tip, by deposition of biomarkers from the capillary rich nail bed, thus allowing measurement by any nail clipping of sufficient weight. Biomarkers are thought to reflect 3-6 months of substance use history in fingernails, and toenails, which grow more slowly, reflect up to 9 months. The detection window (3-6 months) is close to the timeframe of the ASSIST (90 days), making cross-validation by the two measures reasonable.

Approximately 100 mg of nail is required for analysis, which can be obtained from 2mm (a quarter's width) of nail from each of ten digits. Samples will be mailed from home and thus un-observed, and participants will be provided with kits for the nail clipping, and a financial incentive of $30 for providing each of the samples. We will also suggest Veterans set reminders to allow for growth before clippings are needed.

To reduce the risk that Veterans pass off someone else's fingernails as their own, they will be asked if the nails are theirs, and paid regardless of whether they are. Specimen substitution when there are contingencies for positive urines occurs, but there is no incentive for such false reporting when payment is provided regardless of the sample results. The samples will be mailed in coded envelopes addressed to our group, further reducing the likelihood of submitting someone else's fingernails.

- Samples will be processed at the United States Drug Testing Laboratories (Illinois). After processing, samples will be destroyed following a standard storage period. Sample analysis uses fully validated methods that have been inspected and approved by the College of American Pathologists Forensic Drug Testing Program and the New York State Department of Health. Substance Use Treatment Service Utilization-VA Records. Visits from the EHR involving substance use treatment will be identified conservatively, using an algorithm involving workload information entered at clinic visits (e.g. diagnosis treated, procedure performed) and the type of clinic providing the treatment. The measure does not capture much substance abuse counseling in primary care settings, and in conjunction with other mental health treatment (i.e., PTSD treatment). For this reason, self-reported substance use service utilization will be collected (see below).
- Self-Reported Use of Substance Use Treatment Services: Using the same format as the pain treatment service use questions described above, we will inquire about *whether* each of a number of classes of treatments was received in the preceding 12 weeks (substance use counseling, day program, residential, ER/hospital, self-help, counseling at a medical visit, counseling at a visit for a psychiatric condition, opioid substitution, smoking cessation counseling, nicotine replacement therapy prescribed).
- Alcohol Use Disorders Identification Test (AUDIT-C)[128]. This is an alcohol screen used to identify patients who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence). It consists of three questions: "how often did you have a drink containing alcohol in the past year?", "how many drinks did you have on a typical day when you were drinking in the past year", and "how often did you have six or more drinks on one occasion in the past year". It is scored on a scale of 0 (no use) through 12. In men, a score of 4 or more is considered positive and in women, a score of 3 or more is considered positive.

Other Measures:

- Patient Health Questionnaire (PHQ-9). The PHQ-9 is a well validated screening measure for depression[129] and will be used to identify probable depression as a covariate in analyses. It will also identify suicidal ideation, which if severe, will trigger the need for further assessment (detailed in Human Subjects).
- EQ-5D-5L. The EQ-5D-5L is a standardized measure of health status designed to provide a single index value of health for clinical and economic appraisals. It consists of five questions in the domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. .[130]
- Motivation for engaging in pain treatment[131,132]. Motivation for Change Scale to include 3 items (analogue scale coded from 1 to 100) tapping patient likelihood to engage in pain services, recognition of pain treatments as important, and pain treatment motivation.
- COVID-19 questionnaire. These questions will assess participant infection status, adherence to COVID-19 safety regulations, and the effect that COVID-19 regulations have had on Veterans' social determinants of health, access to pain treatment, and access to substance use treatment.

Qualitative Measures Collected in UG3 Phase and then again at the end of the UH3 Phase:

- Relational Coordination Survey. This survey, will be administered post-trial to "hub" SBIRT-PM clinicians and "spoke" clinical and administrative staff in Compensation and Pension and Primary Care to examine how pain care was coordinated to meet the treatment needs of compensation-seeking Veterans. It includes seven dimensions: frequency of communication, timeliness of communication, accuracy of communication, problem-solving, shared goals, shared knowledge, mutual respect). Respondents indicate the frequency in which each dimension exists in their setting on a 5-point scale. The mean of the individual scores serves as the overall RC score for each dimension within each spoke site.
- Post-Trial Semi-Structured Qualitative Interview. At the end of the trial, we will conduct in-depth interviews with "hub" SBIRT clinicians and "spoke" clinical and administrative staff in Compensation and Pension and Primary Care to assess the organization and coordination of pain management services, given their experiences with SBIRT-PM implementation.

Randomization

The urn randomization covariates are: site (8 sites of VISN1), sex (M/F), race (White, Black, Other), ethnicity (Hispanic/Non-Hispanic), and self-reported illicit drug use (Yes/No). Following enrollment and Baseline assessments, the Project Director will enter covariates into urn randomization program to determine intervention condition assignment. Randomization will occur within two weeks of the enrollment date.

6.2.3 Blinding

Research assistants who collect study data will be blind to participants' treatment assignment. Veterans will be instructed during the assessments not to tell the research assistant if they are receiving study counseling. To determine if the blind was maintained, the research assistant will be asked to what condition each Veteran was assigned. The PIs and Project Director will not be blind to randomization, as they will be assigning study therapists to participants randomized to the treatment condition, reviewing counseling sessions for quality/fidelity, and conducting monthly supervision with study counselors. The statistician has no contact with the study veterans; she will not be blinded.

6.2.4 Follow-up Visits

Research assistants will schedule telephone follow-up interviews approximately 12 weeks (+ 4 weeks) and 36 weeks (+ 4 weeks) after baseline visits. A 4-week window for follow-up appointments allows for flexibility in scheduling and provides sufficient time to complete assessments if an appointment is missed.

Week 12 Follow-up
See schedule of evaluations table and descriptions above.

- Distance to nearest VA Facility. We will calculate the driving distance from the Veterans' address to the nearest VA medical facility providing integrated pain services care services. Calculations will be done using google maps.

Week 36 Follow-up
See schedule of evaluations table and descriptions above.

End-of-Study

- Qualitative interview of stakeholders
- Relational Coordinator survey of key stakeholders
- Treatment fidelity: Independent Tape Rater Scale

6.2.5 Completion/Final Evaluation

Participants' final visit is the Week 36 follow-up. Participants will be contacted for week 12 and 36 follow-up visits regardless of whether they engaged in study counseling. If the 12-week follow-up visit is missed and not completed within 4 weeks of the appointment date, that follow-up will be missed and participant will be contacted for final week 36 follow-up visit.

Participation in study assessments and study counseling is voluntary. Participants can participate in study assessments and choose not to engage in counseling. Reasons for terminating a participant prior to week 36 are:

- Participant is found to not be eligible for the study after enrollment
- Participant withdraws consent for further contact

7. SAFETY ASSESSMENTS

The risk to Veterans who participate in this study is minimal. Nevertheless, research staff will be trained in the detection and investigation of adverse events during the conduct of study assessments or other interactions with participants.

Expected adverse experiences include:

- Counseling session or study procedures upsets participant
  Criteria for management: Careful training of study staff and SBIRT-PM counselors will precede study initiation. If a participant complains about study procedures or counseling sessions, the complaint will be logged and will be brought to the attention of the mPIs. Depending on the nature of the complaint, mPIs will decide whether the complaint requires follow-up directly with the participant.

- Suicidal ideation detected by the PHQ-9 or by counseling
  Criteria for management: item 9 in the PHQ-9 identifies potential suicidal ideation (the questions asks about "thoughts of being better off dead or of hurting yourself in some way"). It is collected at baseline and at 12- and 36-week follow-ups. Any positive response (response other than "none at all") to this question will be further evaluated, as well as other expressions of suicidality to the research assistant or SBIRT-PM clinician. Positive responses will be evaluated by one of the mPIs, Site-PIs, or covering providers. The response to clinical emergencies will be delineated in the Service Use Agreements between the hub site and spoke for provision of SBIRT-PM. If the research team decides that the information must be reported, the person who spoke to the Veteran (clinician or research assistant) will contact the Site-PI from the relevant medical center, and if he or she is not available, the clinician designated by the spoke site for handling mental health crises at the sites. All VISN1 medical centers have emergency room facilities and a suicide prevention coordination team. If the participant's situation precludes management by spoke personnel (e.g. the Veteran is not accessible to VA staff or the site PI), the Research Assistant will immediately consult with one of the mPIs about ways to handle the situation, including calling for a police safety check on the Veteran.

7.1 Specification of Safety Parameters

NA.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Unanticipated problems will be recorded as they are discovered throughout the study. The Project Director will record all reportable events with start dates occurring any time after informed consent is obtained until the last day of study participation (approximately 36 weeks after baseline). At each study visit (Baseline, week 12, week 36), the study team will inquire about the occurrence of AE/SAEs since the last visit.

Our group completed a randomized controlled trial of 101 participants to a face-to-face version of SBIRT-PM or two control conditions in a very similar population to that

proposed in this application (Rosen et al., 2018). There were no study-related adverse events in that study, and they are unlikely in this study as well.

7.3 Adverse Events and Serious Adverse Events

An adverse event (AE) is any untoward medical occurrence in a subject during participation in the research study. Veterans with MSD have a high frequency of medical and psychiatric difficulties. Therefore, changes in medication regimen, the presence of medication side effects and symptom exacerbations are not untoward and do not constitute adverse events.

Anticipated adverse events include complaints about the study procedures and the counseling intervention, and any occurrence in which the patient attributes discomfort, harm or disability to the study procedures.

Serious adverse events (SAEs) are adverse events that result in: death, a life-threatening experience, hospitalization, or the need for medical, surgical, behavioral, social or other interventions to prevent such outcomes. Any report that a patient required overnight treatment in any facility (emergency room, detoxification, and hospitalization) will constitute a SAE. Hospitalization or death of another individual due to direct action of patient will also be considered a SAE.

7.4 Reporting Procedures

When an AE or SAE is reported by a participant, we will ask for clarifying information describing the event. Any SAEs will be immediately reported to Dr. Rosen and, if he is unavailable, to Dr. Martino. Reports to Dr. Rosen will include a description of the event and a summary of recent contacts with the patient. This summary will include any warning signs of the adverse event, the patient's general state and any information suggesting a causal link between study participation and the event.

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitor(s), IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator becoming aware of the event.
- Other unexpected SAEs that are related or probably study related will be reported to the IRB, NCCIH Program Officer, and Independent Safety Monitor(s) within 5 days.
- SAEs and AEs that do not meet criteria for reporting within five working days in accordance with VHA Handbook 1058.01 will be reported to the Central IRB and the Independent Safety Monitor(s),at the time of continuing review (overall total and summary of types of events that occurred) in accordance with their requirements. Such events will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

7.5 Follow-up for Adverse Events

The response to clinical emergencies will be delineated in the Service Use Agreements between the hub site and spoke for provision of SBIRT-PM. All VISN1 medical centers have emergency room facilities and a suicide prevention coordination team. If the participant's situation precludes management by spoke personnel (e.g. the Veteran is not accessible to VA staff or the site PI), the Research Assistant will immediately consult with one of the mPIs about ways to handle the situation, including calling for a police safety check on the Veteran.

7.6 Safety Monitoring

A Data and Safety Monitoring Committee (DSMC) will be appointed by NCCIH to review study progress, assess the adequacy of ongoing enrollment & site performance, ensure adequacy of data acquisition & protocol adherence and evaluate overall safety throughout trial implementation. The DSMC will meet at least annually after trial initiation. A DSMC Charter Document outlining the operating guidelines for the committee, the frequency of planned meetings and the specific data presentation format will be agreed upon during the initial meeting of the DSMC. Study reports will be created by the study data center, following a standardized format, as directed by the DSMC. The DSMC will report directly to NCCIH.

Study progress and safety will be reviewed annually during the RCT. Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the DSMB annually. This Annual Report will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated objectives of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor(s) and will be forwarded to the VA Central IRB and the NCCIH Program Officer within 1 month of each monitoring review.

8. INTERVENTION DISCONTINUATION

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The pragmatic two-arm, parallel groups 36-week randomized controlled single blind trial design was selected based on findings from a completed pilot study (Rosen et al., 2018). The study design parameters---components of the intervention and its duration, duration of follow-up, and effect size estimates---were largely derived from that study. Treatment-as-usual was selected as a control condition because the question to be answered by this pragmatic trial is whether the intervention is more effective than the status quo.

Our main objective is to test the effectiveness of SBIRT-PM, compared to Usual Care (UC), when delivered within a VISN1-wide hub-and-spoke network.

Hypothesis 1: SBIRT-PM will be more effective than UC in reducing pain severity as measured by the Brief Pain Inventory (primary outcome #1).

Hypothesis 2: SBIRT-PM will be more effective than UC in reducing the number of substances categorized as requiring any intervention (primary outcome #2) as identified by either self-report (ASSIST) or toxicological analysis of nail clippings.

9.2 Sample Size and Randomization

Given there are two primary outcomes (change in pain severity from the BPI, change in the number of substances whose use requires intervention based on the ASSIST), Bonferroni correction was used to generate a p-value of .025 for the sample size calculations for each outcome.

The planned (randomized) sample size is 1100 with sample selection at each site proportional to the size of the site. This sample size was based on power=.90 using alpha=.025, and an expected ES of d=.25 for pain severity. Breakdown as follows: 400 per group divided by '1 – loss to follow-up' (73%) = 548 x 2 groups= 1096. Clustering was removed from the calculation per the advice of the PMC3 Biostatistics workgroup leadership during our protocol review. Instead, site will be controlled in analyses and a site by treatment interaction effect tested. In addition, power was increased to 90% based on their advice.

The planned sample size allows for 27% attrition. Values are based on previous related work and our 12-week pilot study. In Poisson modeling of our pilot data, SBIRT was associated with a baseline-adjusted relative rate of pain-related appointments attended (a proposed mediator of SBIRT-PM) of RR (Exp(B))=1.6.

For substance use, the proportion converting to low risk on at least one substance in the treatment group was estimated as 27% and in UC as 10%. Attrition was set at 27%. For 90% power (alpha=.025), the calculations resulted in sample size of 128 per group divided by '1 – loss to follow-up' (73%) = 176 x 2 groups= 352 as the total sample size. Given the sample size required for the pain outcome, a small effect size (absolute value of 6% between groups) would be detectable for the substance use outcome with 90% power. In the UG3 pilot study, 67% of the participants at baseline self-reported on the ASSIST a level of risky substance use (either alcohol, tobacco or other drugs) that would require intervention and 33% reported risky alcohol use. Projected to the full trial, this suggests 737 participants are likely to have a clinically significant problem with at least one substance and 357 will have a problem with

alcohol. Thus, we will have an adequate sample in the UH3 RCT to detect changes in our primary substance use outcome.

Treatment Assignment Procedures

The unit of randomization is participant. Participants will be randomized to SBIRT or Usual Care using a computerized urn randomization program within each site to increase the likelihood of balanced allocation of participants to the two interventions on several covariates: sex (male/female), race (White, Black), ethnicity (Hispanic/Non-Hispanic), and self-reported illicit drug use within 90 days (Yes/No). All randomization will be done by the Project Director.

Urn randomization preserves randomization as the primary basis for assignment to treatment and is less susceptible to experimenter bias or manipulation of the allocation process by staff than is balancing. The urn randomization algorithm allows probability of assignment to fluctuate as a function of the degree of covariate imbalance. As a study's sample size increases, urn and simple randomization converge because the treatment assignment probabilities under urn randomization converge asymptotically to the simple randomization probabilities.

Blinding

Research assistants who collect study data will be blind to participants' treatment assignment. Veterans will be instructed during the assessments not to tell the research assistant if they are receiving study counseling. To determine if the blind was maintained, the research assistant will be asked to what condition each Veteran was assigned.

The PIs and Project Director will not be blind to randomization, as they will be assigning study therapists to participants randomized to the treatment condition, reviewing counseling sessions for quality/fidelity, and conducting monthly supervision with study counselors. The statistician has no contact with the study veterans; she will not be blinded.

9.3 Definition of Populations

The study will occur within the eight VISN-1 VA medical centers (VAMC) located across six New England States. The medical centers are: Bedford VAMC; Boston Healthcare System; Central Western Massachusetts; Connecticut Healthcare System; Maine Healthcare System, Manchester VAMC, Providence VAMC, and White River Junction.

Inclusion and exclusion criteria:

Inclusion criteria: 1) post-9/11 Veteran applying for MSD-related compensation (specified as back, neck, shoulder, or knee pain), as ascertained from filed claim, 2) reports a score of ≥4 (threshold for moderately severe pain) on the BPI's Pain Severity subscale (average of four pain intensity items); 3) availability of a landline or cellular telephone for SBIRT-PM.

Exclusion criteria: 1) reports inability to participate during the study enrollment call; 2) received three or more non-pharmacological pain treatment modalities within the last 12 weeks from VA, and 3) participation in another PMC3 study as evidenced by a research protocol alert for that study at the time the study invitation letter is mailed.

Participants who complete the baseline assessment and are randomized to their treatment assignment will be the Intent to treat (ITT) population for analysis. The per-protocol analyses will specify patients who participated the treatment and be conducted by including a variable indicating participation (Yes/No) in the ITT analyses. We will give precedence to the results of the ITT analysis over the PP analysis.

9.4 Interim Analyses and Stopping Rules

No interim analysis is planned. An in-person version of the proposed intervention was tested in a completed study by this team (Rosen et al., 2018). There were no study-related adverse events.

There are no stopping rules.

9.5 Outcomes

9.5.1 Primary Outcome

The two primary outcomes are pain severity as measured by the BPI and the number of substances above the “no intervention” threshold in the ASSIST. We initially planned that when a positive toxicology result disagrees with a self-report of no use, the middle value on the ordinal scale (the indication to receive brief intervention) would be derived and used as the primary substance use outcome. However, only 64% of participants returned nail samples at baseline, and this percentage dropped to 58% and 49% at week 12 and 36, respectively, among participants with completed ASSIST assessments. Further, depending upon the substance and timepoint, between 43% and 48% of participants self-reporting a level of substance use that does not require an intervention, the group whose substance use classification would change with positive nail toxicology, did not have toxicology results. Given the amount of missing toxicology data and that nails do not measure intervention need directly like the ASSIST, we plan to base our primary substance use outcome on the ASSIST measure only. This change does not compromise our estimated power since the number of participants self-reporting a level of risky substance use that requires an intervention on the ASSIST (N=571) exceeds our assumed total sample size for this outcome (N=352) used in power analyses. The BPI and ASSIST are collected at baseline, week 12 and week 36.

9.5.2 Secondary Outcomes

Secondary outcomes related to pain include non-pharmacological pain management service utilization, pain interference with life activities (BPI), overall pain (PEG), and overall health. The non-pharmacological pain management service utilization will be

summed across 13 possible modalities (injection; physical therapy; chiropractic care; acupuncture; TENS; Spinal cord stimulator; cognitive behavioral therapy; mindfulness/acceptance and community therapy; treatment involving teaching about coping with pain; yoga, Tai chi or Reiki; massage treatment; other treatment not already mentioned) as well as examined by individual modalities where sufficient sample size is present.

Secondary outcomes related to substance use will include severity measures for individual substances generated by the ASSIST, as well as toxicology results for individual substances.

9.6 Data Analyses

All variables (Intervention, covariates and outcomes) will be described with the use of the approximate summary statistics (mean, median, interquartile range, and percent). Multivariate models will be used following the examination of bivariate tests of outcomes by intervention group. A successful outcome will be either a reduction in pain severity or number of substance use above the “no intervention” threshold in the ASSIST or toxicological analysis of nail clippings. The model type will be selected based on meeting of modeling assumptions including the outcome distribution; Potential models will include linear and non-linear mixed-effects (Poisson (with over-dispersion), negative binomial, binary outcome) regression modeling. If there is a large skew with many zeros (which is quite possible where the outcome is change in the number of substances no longer needing intervention), we will use a negative binomial. If the distribution is a combination of 0’s (no change) and 1’s (change to level of “no need for intervention” in one substance) with very few outcomes greater than 1, a binomial distribution will likely be used. A Poisson model will be used if there are very few successes and they have a Poisson distribution.

These common rules will be used for guidance:

- Poisson distribution, if mean = variance
- Binomial distribution, if mean > variance
- Negative binomial distribution, if mean < variance

The covariance structures will be explored to determine which (unstructured, compound symmetry, autoregressive) is the most appropriate in mixed models. Selection will be based on the lowest AIC. An intervention by time interaction will be tested in the models – this will show the effect of the intervention on the outcome compared to controls.

Change in Pain: We anticipate using linear mixed-effects modeling to test the effect of SBIRT-PM on the 12-week value of the BPI, if it is a normally distributed outcome. We will in addition test simultaneously the unique effects of treatment on pain outcomes at week 12 and week 36, controlling for baseline differences, and test the equality of these parameters using the Wald test.

Change in Substance Use: We anticipate using non-linear mixed-effects (Poisson, negative binomial, binary outcome as discussed above) regression modeling to test the effect of SBIRT-PM on the number of substances requiring intervention (according to the ASSIST), a count outcome. One subset of analyses will use risk sets

(at least 1 substance at baseline, at least 2 substances at baseline, etc.) to analyze substance risk changes in substance users. We will also test the equality of treatment effects at weeks 12 and 36 as described above.

We have identified stratification variables to account for error variance as a recommended good practice. Key covariates to be included in the model are depression, TBI, and mental health diagnoses (grouped into multiple more homogenous groupings, such as mood and psychotic disorders) as these are highly related to pain perception and substance abuse as well as the urn covariates– namely sex, race, ethnicity, self-reported illicit drug use and site. The strata used for the urn randomization are only to better ensure balance on key characteristics. Their main effects will not be interpreted in the analysis, though they will be examined as potential modifiers of the intervention effect. We will also consider as potential covariates: distance to nearest VA medical center, number of pain treatment modalities used at baseline, reasons patient might drop out of the study, and the probability of withdrawal. Opioid-use will be examined as a mediator as well as a tertiary outcome. Actual participation in SBIRT-PM (Y/N) will be examined as a mediator of response.

Per NIH policy, because there is considerable data suggesting the importance of race, ethnicity and sex on the study outcomes (pain, substance use and service use), we will conduct an analysis that examines sex and race/ethnicity as moderators of treatment response. These analyses will be conducted through the inclusion of interaction effects in models so sex and race/ethnicity effects can be formally tested. In light of the differences in substance use, body habitus, and substance metabolism between men and women, we will include a sex interaction term for the analysis of the relationship between self-reported levels of substance use and levels of ETG found in nail clippings. While the use of subgroup analysis might be interesting to look at sex-specific characteristics such as the influence of pregnancy or stage of menstrual cycle, we currently have no relevant covariates making the case for this type of sub-analysis.

Sensitivity Analysis

We anticipate some missingness will occur not completely at random. In general, more sensitive information such as use of illicit substances is less likely to be shared by participants when responding to an interviewer. Based on our previous study (R34), we anticipate there might be a difference in the follow-up rate between Veterans in the two arms of the trial, with veterans in the usual care arm more frequently dropping out. We have created scenarios to minimize missing data through design considerations (i.e., increasing our payment scale as incentive, regular reminder calls), but our analytic plan includes the investigation of missingness. Patterns of missingness will be examined by each individual covariate in the data (univariate, monotone or non-monotone). Chi-squares and t-tests will be run to see if missingness is related to other variables in the analysis (for example: intervention status, substance use). We intend to utilize multiple imputation in the case of variables missing either completely at random or at random. To reduce the likelihood of MNAR, the multiple imputation model will include “auxiliary variables” which are highly correlated with both the variable that has missing data and the probability that the variable is missing. Sensitivity analyses will be conducted as part of the multiple imputation procedure in SAS 9.4 (PROC MI).

Sources of data

Data for the study are drawn from patient self-report, VA electronic medical records of VA and community care, and the C&P examination. Veterans requesting a Compensation & Pension evaluation for knee, shoulder, neck or back pain may or not be receiving services from the VA. Persons who get all their care outside of the VA will not have readily accessible medical records, while those persons who get some care in the VA but are sent out to community care for distinct services (such as non-pharmacological pain management) will have medical records of both types of care. In addition, those veterans who had not used any VA services prior to their C&P request may then enter VA care following their C&P exam and will have EMR available only in the follow-up period. The lack of EMR data of non-users of the VA will affect both the intervention or control arms of the study, and there is no reason to believe its effect will be differential.

Acknowledging the variability in availability of EMR information, all subjects will have self-reported and C&P data regarding service use as well as diagnoses. We will examine the concordance of self-reported and EMR-obtained information to estimate the impact of having no EMR data in the non-users of the VA. We will conduct a sensitivity analysis sub-setting the analyses only to those persons with available EMR (as well as self-reported and C&P data).

Cost-Effectiveness Analysis

The relative cost-effectiveness of SBIRT-PM will be assessed using both incremental cost-effectiveness ratios (ICERs) and cost-effectiveness acceptability curves (CEACs). ICERs and CEACs will be calculated from the provider (i.e., VISN and medical center) perspective. Using the cost estimates described in the Assessment subsection, we will calculate ICERs for minimal clinically important differences (MCID) between baseline and week-36 assessments in three primary outcomes: self-reported pain, risky alcohol use, and morphine-equivalent doses of opioid analgesic medication use.

- Pain. Self-reported pain severity and interference will be measured by the Brief Pain Inventory (BPI). A MCID in pain severity will be a 30% reduction in ratings on this BPI subscale from baseline to week 36. The MCID for pain functioning will be a 1-point change in the BPI pain interference subscale. We have followed the guidelines Erin Krebs followed in the SPACE trial for selecting an MCID. She states in her group's 2018 JAMA report of the SPACE trial: "Following consensus guidelines, this trial used a 1-point difference as the MCID for BPI interference and BPI severity, and used a 30% reduction from baseline as MCID for moderate improvement."
- Substance Use. As noted earlier, the ASSIST categories represent what clinicians consider a clinically important difference, in that a difference the differences in risk category guide treatment. Therefore, we will consider a net decrease of one risk category (i.e. need for less overall treatment) across substances as the MCID.

The ICERs will measure the incremental cost of using SBIRT-PM to produce a MCID in each of the outcomes. We will conclude SBIRT-PM's cost-effectiveness for each outcome based on its ICER with respect to the threshold value placed by decision makers on the effect for that outcome. By using multiple outcomes, we can determine

the robustness of our cost-effectiveness findings and provide a more fine-grained cost-effectiveness analysis to address different priorities that stakeholders may have.[186, 187]

To illustrate the uncertainty associated with ICER point estimates, cost and effect estimates of SBIRT-PM will be bootstrapped (with 2,000 replicates) to produce confidence intervals around the ICERs and to produce CEACs for each outcome measure.[188] CEACs quantify the uncertainty in the cost-effectiveness analysis by showing the probability that the intervention is cost-effective with respect to any given threshold value.[188-190] Intuitively, as the threshold value of a MCID in a given outcome increases, the strategy that produces that effect most efficiently becomes increasingly more likely to be the most cost effective, even though incremental costs are incurred. Similarly, as the threshold value of a MCID in a given outcome decreases, the strategy that has the lowest cost becomes increasingly more likely to be the most cost-effective. Finally, sensitivity analyses will be conducted to determine the robustness of the cost-effectiveness results to alternative assumptions about a wide variety of implementation parameters (e.g., cost of inputs).

Budget Impact Analysis.

To demonstrate the financial feasibility of adopting SBIRT-PM, a budget impact analysis will be conducted. The per-person cost of SBIRT-PM will comprise the cost of delivering the intervention plus the cost of the VA-funded services used by the participant in the SBIRT-PM condition over and above the cost of those used by individuals in UC, minus the yearly patient allocation (VERA dollars) assigned to that participant. The total projected yearly cost to a given medical center of SBIRT-PM will be the per-person cost times the total number of Veterans applying for compensation and pension for a musculoskeletal condition times the expected rate of uptake.

Analyses of NLP Algorithms

We will identify the use of non-pharmacological pain modalities through self-report from the participants as well as two different approaches to the extraction of healthcare utilization data from electronic medical records. Medical record extraction of 1.) Structured data - stop codes indicating use of these modalities, and 2.) Unstructured data - domains identified in the application of the NLP method to the medical record data of study participants. Two independent researchers will identify words/snippets that suggest use of specific non-pharma modalities and rate enough snippets to have software reliably generate an algorithm to rate all patients included in the study on each modality (machine learning). As we expect false positive reports of use of a modality to be unlikely, identification of use during an assessment period by any of the three methods (self-report, medical record stop codes and NLP) will be considered use. The agreement between these different measures will be described by cross-tabs.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Research Assistants will screen and collect contact information for all study subjects on the “Participant Screening and Contacts Form”. Information will be collected by

Research Assistants over the telephone and entered directly into the electronic form. Forms are saved in a restricted research folder on secure VA networked computers.

Research Assistants will collect all baseline and follow-up interview data by telephone interview with the participants. They will enter data directly into REDCap questionnaires. Research assistants are blind to participant's randomization group. REDCap questionnaires and data are saved in VA REDCap and in a restricted research folder on secure VA networked computers. VA REDCap can only be accessed on the secure VA Network.

Electronic medical record data will be accessed and stored on the VA Informatics and Computing Infrastructure (VINCI) platform and in a restricted research folder on secure VA networked computers.

10.2 Data Management

VA REDCap is a secure web application for building and managing online surveys that can be used for direct data entry by Research Staff. Project questionnaires will be created and used for data collection. After data are collected, REDCap provides automated export procedures for data to be downloaded to Excel and common statistical packages (SPSS, SAS, R) for data analysis. In these programs, filters flag data that needs to be re-checked by a person such as unclear characters, out-of-range variables and logical inconsistencies. The project director and project statistician will check files monthly so that errors can be readily corrected and consequential differences between treatment types (e.g., different levels of attrition) can be monitored closely.

10.3 Quality Assurance

10.3.1 Training

Training of Study Counselors

Dr. Martino will provide competency-based supervision to support the counselors' delivery of SBIRT-PM throughout the trial. This approach is consistent with the national VA Evidence-Based Practice training model,[95] which emphasizes extended post-workshop case-based supervision or consultation, including submission of audio recorded therapy sessions for treatment fidelity review, as an essential training component. Dr. Martino will meet with the counselors together on a 1-hour monthly basis to review their SBIRT-PM practice. For these supervision meetings, he will listen to and rate the clinicians' SBIRT-PM fidelity for two sessions per counselor (one initial and one follow-up call) using the Independent Tape Rater Scale [96] for the purposes of feedback and coaching during supervision. In MI clinician training research, this approach and dose of supervision has been shown to sustain proficient practice.[97]

The risk of angering or alienating Veterans is low because of the non-confrontational nature of SBIRT-PM. The risk will be further minimized by hiring experienced counselors who have experience with the study population. Study counselors will be trained to adopt a collaborative approach. Study counselors will also be knowledgeable about the location of emergency rooms, VA Police, and crisis

services available at each VISN1 medical center, as well as mandated reporting procedures for all sites.

Training of Study Research Assistant

Staff obtaining verbal consent will have completed a web-based course with post-test on Human Research Protections, and all will have had specific training by the mPIs in obtaining informed consent for this project.

The research assistant will receive training in the study assessments from the Project Director and the two mPIs. The research assistants will administer the study consent and assessments to other staff in role plays until they are administered correctly. Research assistants will be asked to contact the PIs about participant responses that are not obvious to code within the offered choice options.

The research assistant will also be knowledgeable about the emergency facilities (emergency rooms, VA Police, and crisis services) at each VISN1 medical center. The research assistant will also receive training in de-escalating agitated Veterans.

COVID-19 response: the research assistants collecting self-report data about pain and substance use service utilization will prompt veterans to consider in-person and all telehealth/virtual and telephone-delivered services when responding to our service utilization assessment.

10.3.2 Quality Control Committee

NA

10.3.3 Metrics

Study progress and safety will be reviewed monthly by the mPIs and Project Director. An Annual Report will be sent to the Independent Monitor(s) and will be forwarded to the VA Central IRB and the NCCIH Program Officer within 1 month of each monitoring review.

Data type	Frequency of review	Reviewer
Subject accrual (including compliance with protocol enrollment criteria)	Monthly	PI, Project Director
	Annually	DSMB
Status of all enrolled subjects, as of date of reporting	Monthly	PI, Project Director
	Annually	DSMB
Data entry quality control checks on 10% of charts These checks will consist of verifying that there is no missing data (except for patient refusals for specific items) and all assessments are completed. In REDCap, if a question is not answered, a box will pop up highlighting the unanswered questions before it allows the RA to “complete” the form. This will allow veterans to answer any missing items	Monthly	Project Director

during the same telephone call. If a question is refused by the veteran it will be left blank and the RA will put a note in saying it was refused.		
Adherence data regarding study visits and intervention	Monthly	PI, Project Director
	Annually	DSMB
AEs and rates	Monthly	PI, Project Director
	Annually	DSMB
	Annually	NCCIH, VA Central IRB
SAEs (unexpected and related)	Per occurrence	PI, DSMB, NIH/NCCIH
SAEs (expected or unrelated)	Per Occurrence	PI, Project Director
	Annually	DSMB, NIH/NCCIH
Unanticipated Problems	Per Occurrence	PI, Project Director
	Per Policy	VA Central IRB

10.3.4 Protocol Deviations

Protocol deviations will be reported to mPIs as they are discovered. mPIs will report protocol deviations to the VA Central IRB according to cIRB policies.

10.3.5 Monitoring

The Project Director will create study checklists for each data collection point to ensure data is collected as outlined in the approved protocol. All self-reported survey data will be collected directly in VA REDCap. VA REDCap is a secure web application for building and managing online surveys that can be used for direct data entry by Research Staff. Project questionnaires can be created and used for data collection. After data are collected, REDCap provides automated export procedures for data to be downloaded to Excel and common statistical packages (SPSS, SAS, R) for data analysis. In these programs, filters flag data that needs to be re-checked by a person such as unclear characters, out-of-range variables and logical inconsistencies. The Project Director will check files monthly so that errors can be readily corrected and consequential differences between treatment types (e.g., different levels of attrition) can be monitored closely. Data quality will be monitored by random inspection of the completed forms monthly by the Project Director and any problems detected will be discussed with the mPIs. Recruitment and retention data will be reviewed and reported to study leadership monthly.

We will collect data about SBIRT-PM implementation. Specifically, we will report the percentage of participants who received different “doses” of the intervention (i.,e., 0, 1, 2, 3, or 4 sessions). We also will track the percentage of each counselor’s assigned Veterans who receive counseling and the percentage whose first counseling session is

followed by a second. In our pilot, 80% of participants received the assigned counseling, and 55% of those who received any counseling had at least two sessions. If a counselor falls below 70% of participants receiving any counseling within 12 weeks or below 50% of a second session among those with a first, we will take the following steps: 1) compare that counselor's procedures to "best practices" by other counselors. Such best practices might include time of day Veterans are called, and the negotiation around scheduling the calls; and 2) contact the site PI to determine if sub-optimal engagement is a site-specific issue. Two examples of site-specific issues are cell phone reception and local VA hospital reputations. In very rural areas, poor cell phone coverage makes participation more difficult, and it may be more difficult to engage Veterans when the VA facilities in their local communities have a damaged reputation.

Clinicians will receive standardized training for SBIRT-PM, with their fidelity monitored by Dr. Martino using a competency-based supervision approach. We will independently rate a random sample of about 10% of the SBIRT-PM sessions (n = 220) for the counselors' adherence and competence in delivering the intervention using the Independent Tape Rater Scale. The ITRS has two factors - fundamental and advanced motivational interviewing strategies, as well as a clinical consensus-based benchmark of adequate proficiency, namely, half of the 10 motivational interviewing consistent items being rated $\geq$ 4 for both adherence and competence. We will report the mean factor scores for adherence and competence, as well as the percentage of sessions that meet adequate proficiency standards in the random sample as a reflection of our success in implementing SBIT-PM during the trial. To support high-integrity implementation during the trial, Dr. Martino will review two sessions per counselor per month using the ITRS and provide feedback and coaching to the counselors in monthly supervision meetings. Should a counselor fall below an adequate level of performance on two consecutive sessions reviewed by Dr. Martino, he will review one session per week from that counselor and meet with the counselor individually for more intensive supervision until the counselor's proficiency reaches adequate or better standards once again.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

11.1 Institutional Review Board (IRB) Review

The VA Central IRB has approved the study application (containing a VA Central IRB

protocol, waivers, application forms, etc.). Any subsequent modifications will be reviewed and approved by the VA Central IRB and incorporated into this NCCIH protocol.

11.2 Informed Consent Forms

Veteran Participants

Voluntary informed consent will be obtained from all Veterans prior to participation. Research assistants will conduct the informed consent process with participants over the telephone. The Informed consent process and the participant's agreement to participate will be documented in an audio file.

Veterans will be provided with information about the SBIRT-PM intervention, how long it will last, the nature of study assessments, information about the collection of biological specimens, the examination of their electronic health care and VA data, and potential risks and benefits of study participation. Veterans will be reminded that they can withdraw from the study at any time without penalty. They will be given the opportunity to ask questions and then will be asked if they agree to participate.

Veterans who agree to participant will state so for the audio-recording. Audio-recorded consents will be stored on VA Network computers behind the VHA firewall.

VA Staff Participants

Voluntary informed consent will be obtained from all VA staff interviewed for the study prior to participation. For the qualitative interviews, Research staff will describe the purpose of the interview prior to administering these assessments. Participating VA staff members will be encouraged to ask any questions and have the option to discontinue participation without prejudice. They will be approached by people other than their direct supervisors. After a brief reiteration of the study purpose, the interviewer will confirm consent to record the interview for transcription and analysis purposes before proceeding. A waiver of documentation of informed consent for VA staff participants has been obtained. No documentation will be obtained.

For the survey, a survey invitation will be emailed to VA staff directly from REDCap. The invitation will explain the purpose of the survey and who will have access to the results.

11.3 Participant Confidentiality

Privacy and Confidentiality of Veteran Participant Data:
Data Storage - All possible precautions will be taken to prevent a breach of confidentiality.

1. Minimizing PHI in study databases: Research data will be identified by code number and will not include names, although enrollment records must also be kept and these records will include names. Our study forms have been designed to avoid collecting identifiable information; no Protected Health Information (PHI) will be collected on study forms. We collect only protocol session dates. These dates are changed to 'number of sessions completed' when data sets are anonymized and released to other investigators.
2. Data with PHI: Personal identifiers will be retained to obtain VA service use data from central VA databases. The personal identifiers will be used to identify

service use by study participants from the VA central data repositories. Study data will be stored and analyzed on VA secure network computers and in the VA Informatics and Computing Infrastructure (VINCI). VINCI is a Department of Veterans Affairs (VA) Health Services Research & Development (HSR&D) resource center that provides a secure, central analytic platform for performing research and supporting clinical operations activities. It is a partnership between the VA Office of Information Technology (OI&T) and the Veterans Health Administration Office of Research and Development (VHA ORD). VINCI includes a cluster of servers for securely hosting suites of databases integrated from select national VA data sources. VINCI servers for data, applications and virtual sessions are physically located at the VA Austin Information Technology Center (AITC), located in Austin, Texas. This secure enclave with 105 high-performance servers and 1.5 petabytes of high-speed data storage has multiple layers of security and disaster recovery to prevent data loss. To ensure the protection of Veteran 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 are 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. All data transferred from VINCI is subject to audit for compliance. VA-credentialed research staffs are granted access to study-specific data along with tools for analysis and reporting in the secure, virtual working environment through a certified VHA network computer within the VA. If not working within a VA or VHA hosted office environment containing VA network access, researchers may apply for and then access VINCI through an approved Virtual Private Network (VPN) and Remote Desktop application. The remote computing environment enables data analysis to be performed directly on VINCI servers, offering several advantages: uniform security standards for access; a common point of entry for all investigators who use the data; tools for analysis and reporting; tighter and more consistent control of data quality; and the ability to standardize and update terminology and format as technology and methodology improve. After the needed service use information is extracted, the identifiers will be removed to create files with de-identified data for subsequent analyses. At the conclusion of the study, all files with identifiers will be destroyed. The files with identifiers will be stored on VA secure network computers. Data Security will be insured by using servers which all reside completely behind the VA firewall. There is no public internet access. Another layer of protection for sensitive information is ascribed to the system by use of granular access privileges. Only authorized staff will have data access. Study managers have the capability of granting access and read-write privileges to users. All systems undergo daily backup and 24-hour security.

3. Clinical enrollment records are kept separate from research data. Participants' names will appear only on the consent form, HIPAA authorization form, and "key"

form kept by the mPIs. All paper forms will be stored and secured in a locked file cabinet under the jurisdiction of the Dr. Rosen.

4. Presentation of Study Results: The research records will be used to prepare reports that do not allow for the identification of individual study participants.
5. Communication by Research Staff: All computers used by research staff are password protected. All research staff and counselors receive annual Good Clinical Practice, Human Subjects Protection, HIPAA, and VHA privacy training through Yale and the VA. Our data collection and management procedures are fully compliant with HIPAA.

Confidentiality of Digital Audio Recorded Counseling Sessions - To assure the confidentiality and protection of participants with respect to digital audio recording of SBIRT-PM sessions, the following steps will be taken:

1. Participants will provide informed consent for digital audio recording. Participants will be allowed to participate in the study and refuse the audio recording. Participants who do consent to audio recording will be informed that they have the right to stop the audio recording at any time during the session.
2. Digital audio recordings will be treated as confidential research records. They will be labeled with a unique study ID code and uploaded to a secure network VA server, separate from other study data. The audio file name will use study ID codes.
3. Access to audio recordings will be limited to members of the investigative team including trained research raters who will rate the recordings according to the clinician adherence and competence rating system and only the research staff will have access to the recordings. A separate file will link the audio recording file code to the participant's unique identification code, the clinician's name, and the date of the session.

Privacy and Confidentiality of VA Staff Participant Data:
VA staff will have the right to stop the audio recording at any time during the interviews. These recordings will be treated as confidential research records, labeled with unique study ID codes, and uploaded to a secure network VA server. Recorded interviews will be transcribed by VA staff in the Centralized Transcription Service Program (CTSP) in Salt Lake City, UT. THE CTSP ensures VA privacy and security requirements are met by operating within the VA firewall. Both audio recordings and transcriptions will be kept behind the VHA firewall. Access to survey data and recordings will be limited to members of the investigative team in involved in managing, analyzing, and interpreting them.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

NCCIH Protocol Review Committee (PRC) is an external committee appointed by NCCIH to review clinical study documents and provide specific recommendations to NIH.

Pain Management Collaboratory Coordinating Center (PMC3) Steering Committee provides administrative support, project management, quality management and communications between study projects. The committee will address issues that span all projects and provide input into the policies and processes of the NIH-DoD-VA PMC. This includes guiding the demonstration projects and work groups to develop best practices and tools to foster harmonization. Steering Committee Members include Bob Kerns (Chair), Cindy Brant, Peter Peduzzi (Co-PIs), PIs from each demonstration project, work group representatives, NIH, DoD, VA Program Coordinators, Program Officers/Project Scientists, and subject matter experts.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of results from this study's data will be overseen by Drs. Rosen and Martino. Publications that result from data compiled across PMC3 studies will be subject to the PMC3 Collaboration Publication policy.

14. REFERENCES

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15. SUPPLEMENTS/APPENDICES

I. Informed Consent Form Template

VA Central IRB reviewed and approved Information Sheet (v. 11/8/18)
VA Central IRB reviewed and approved Phone Script (v. 11/8/18)

II. VA Central IRB reviewed and approved Protocol (v.11/8/18)