Care Outcomes for Chiropractic Outpatient Veterans (COCOV): Clinical Trial Study Protocol

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Tool Revision History

Version Number: 9
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Summary of Revisions Made:

V2 -Added terminology to reinforce this is a pilot study; bolded appendix call-outs to alert reader to additional information.
-Updated language of inclusion criteria
-Updated data analysis information

V3 -Added Yale Center for Medical Informatics (YCMI) to Participating Study Sites
-Updated sections 10.1 & 10.2
-Added Carrie Franciscus to Support Personnel

V4 -All participants (not 15%) will be given exit interview
-Providers will also be asked to complete an exit interview

V5 -Added Amy Minkalis, Elissa Twist, Greg Boyer, and Tracy Szabo to Support Personnel
-Removed Julie Hartman from Support Personnel
-Changed communication with participants from MyHealtheVet to REDCap

V7 -Page 7 – addition of study coordinator to PM job title
-Page 8 – change of job title for Elissa Twist to assistant study coordinator
-Page 9 – removal of Greg Boyer from research team
-Page 15 – Section 4.1: 4th bullet clarifies inclusion criteria for the 75% who will have a mental health condition
-Page 16 – Section 4.2: Clarification of cut-points for mental health screening tools and procedure if participant answers showing signs of suicidal ideation.
-Page 17 – Section 4.3: Clarification for use of patient information
-Page 18 – Section 4.3: Clarification of recruitment from chiropractic schedule
-Page 24 – Section 6.2: Information on back-up study coordinator
-Page 36 – Section 10.3.2: Steering committee responsibilities clarified
-Page 38 – Section 11.3: Language added for use of study issued mobile device

V8 -removal of the 4 age cohorts to one single cohort of 40 participants 18+

V9 -rewording of roles on title page
-Page 27 – Section 6.2.2: addition of backup study coordinator to be trained and able to complete exit interviews.

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Care Outcomes for Chiropractic Outpatient Veterans (COCOV)

Objectives

The primary objectives of this pilot clinical trial are to evaluate the feasibility, safety and acceptability of an integrative care pathway that includes chiropractic care, for the coordinated care for Veterans Administration (VA) patients with chronic low back pain (cLBP), with an emphasis on those with mental health comorbidity, in preparation for the conduct of an appropriately powered multi-site randomized controlled trial (RCT). The secondary objectives are to collect study outcomes at the baseline visit (BV) and at weeks 3, 5, 7, and 10 to: 1) assess the success of collecting outcomes; 2) determine the outcome measures to use in a future RCT; and 3) determine preliminary intervention effect sizes and variability to aid in sample size determination for a future RCT.

Design and Outcomes

This pilot study is a single-arm clinical trial. All participants will be asked to complete study outcomes which include the Roland Morris Disability Questionnaire (RMDQ), Brief Pain inventory (BPI), as well as the Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder 7-item Scale (GAD-7), Post-traumatic Stress Disorder Checklist-Civilian Version (PLC-C), Alcohol Use Disorders Identification Test (AUDIT), Keele Start Back Screening Tool (STarT Back), self-efficacy for managing symptoms (SF8a), self-care behaviors, Expectations for Complementary and Integrative Treatments Questionnaire (EXPECT), Healing Encounters and Attitudes Lists (HEAL), and Pain Intensity, Enjoyment of Life, General Activity Assessment Tool (PEG) questionnaires, and the Pain Assessment Screening Tool and Outcomes Registry (PASTOR) assessment, includes LBP intensity and interference as measured by the Defense and Veterans Pain Rating Scale (DVPRS), pain, disability, mental health, quality of life enjoyment and satisfaction.

Interventions and Duration

All participants will receive up to 10 weeks of chiropractic care and will complete outcome assessments at weeks 3, 5, 7, and 10 of the study.

Sample Size and Population

This pilot study will recruit 40 veterans aged 18 and older, who have cLBP from the Iowa City VA Health Care System (ICVAHCS) and the Coralville, Iowa Community-Based Outpatient Clinic (C-CBOC), also a VA setting. We plan to enroll 40 participants, some of whom may have a mental health comorbidity.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objectives of this pilot, uncontrolled clinical trial are to evaluate the feasibility, safety and acceptability of an integrative care pathway that includes chiropractic care, for the coordinated care for Veterans Administration (VA) patients with chronic low back pain (cLBP), with an emphasis on those with mental health comorbidity, in preparation for the conduct of an appropriately powered multi-site randomized controlled trial (RCT). Specifically, the pilot will focus on the following:

- Feasibility will be assessed by monitoring recruitment, retention, and visit compliance and assessing trial management protocols and ability to meet regulatory deadlines.
- Safety will be assessed by monitoring Adverse Events (AEs).
- Participant and provider perceptions of the pilot will be assessed with a structured, qualitative exit interview.

1.2 Secondary Objectives

To collect study outcomes (LBP disability, PASTOR, mental health assessments) at the baseline visit (BV) and at weeks 3, 5, 7, and 10 to: 1) assess the success of collecting outcomes; 2) determine the outcome measures to use in a future RCT; and 3) determine preliminary intervention effect sizes and variability to aid in sample size determination for a future RCT.

2. BACKGROUND AND RATIONALE-

2.1 Background on Veterans with Chronic Pain and Mental Health Conditions

The coinciding problems of chronic pain and mental illness are of great concern for patients seeking care within the Department of Veterans Affairs (VA) healthcare facilities.[1-3] Of the 5.7 million veterans treated in VA facilities in 2012, more than half reported chronic pain syndromes,[2] including chronic low back pain (cLBP).[4-9] Veterans also experience many mental health comorbidity, such as depression, anxiety, post-traumatic stress disorder (PTSD), and substance abuse.[10-12] Veterans in pain are often managed using overlapping pain and mental illness with prescription drugs, including opioids, psychotropic medications, and sleep agents.[2;13] These potentially harmful drug combinations, which have demonstrated only nominal positive impact on chronic musculoskeletal (MSK) pain, put veterans at high risk for diminished quality of life, drug addiction, and opioid overdose. Non-pharmacological treatments for chronic pain, which also may provide relief of mental health symptoms, may be welcomed complementary therapies for veterans suffering from these conditions.

2.2 Study Rationale

In addition to developing solutions to the critical issue of non-pharmacological pain management for veterans with comorbid pain and mental health conditions, the COCOV clinical trial planning grant addresses multiple aspects of 2 intentions from the 2016 NCCIH Strategic Plan.

1: Advance fundamental science and methods development.

- This trial will assess PASTOR, which includes numerous Patient-Reported Outcomes Measurement Information System (PROMIS)-based instruments, using innovative electronic data collection methods and compare the utility of these new measures against legacy instruments in the veteran population.

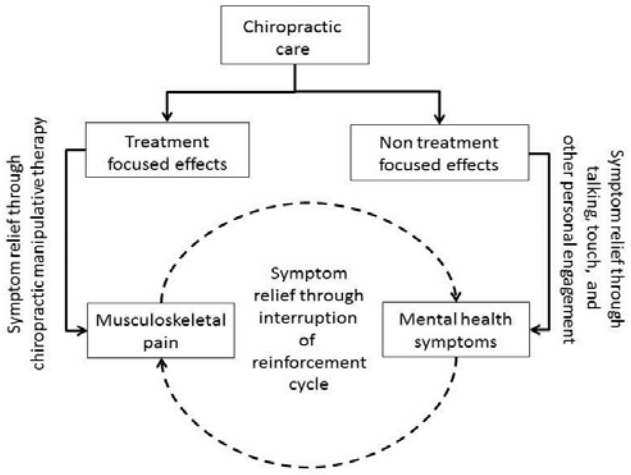
2: Improve care for hard-to-manage symptoms.

- This trial will evaluate an integrative care pathway that includes chiropractic care for the treatment of cLBP with mental health comorbidity (depression, anxiety and PTSD).
- This trial will be conducted in the "real world" clinical setting of a VA healthcare facility and will test the safety and efficacy of chiropractic care for patients with active mental health comorbidity, a population often excluded from RCTs of manual therapies.

The DoD/VA Pain Management Task Force has adopted a team-based, stepped-care model that combines pharmacological strategies for pain management with complementary and integrative health (CIH) modalities.[2] Chiropractic care, one such CIH therapy, has demonstrated evidence of efficacy and safety for the management of pain and disability for LBP and other MSK disorders.[14;15] Within the DoD/VA model, chiropractic care is a Tier 1 treatment modality, which pairs clinic-based spinal manipulative therapy (SMT, considered a passive therapy in the DoD/VA model) with self-correcting exercises (active therapy) for patients with pain.[1] Few studies have evaluated the efficacy of chiropractic care for veterans' experiencing pain, disability, or mental health conditions.[16-20]

The conceptual model for the potential relationship between chiropractic care and relief of MSK pain and mental health symptoms is depicted in **Figure 1**. Patients with MSK pain and pain at multiple locations often report depression, anxiety and other mental health symptoms.[21] Chronic pain may perpetuate mental health comorbidity as these conditions share common pathophysiological pathways.[22;23] Research has shown that the non-specific effects of empathetic doctor communication and therapeutic alliance improves clinical outcomes.[24-28] We hypothesize that chiropractic care offers relief for pain and mental health symptoms through the direct effects of treatment-focused CMT, as well as through the indirect, non-specific effects of the team-based relationship with the clinician.

Figure 1. Conceptual model of the potential relationship between chiropractic care and relief of musculoskeletal pain and mental health symptoms



However, chiropractic care is not delivered in isolation from other treatments within the VA. Thus, we will test a feasible, effective, patient-centered, guideline-based, integrative care model that integrates chiropractic into VA Patient Aligned Care Teams (PACTs). This integrative care pathway will involve primary care providers, mental health professionals, and doctors of chiropractic (DCs) engaged in the treatment of veterans with cLBP, with or without mental health comorbidity. While DCs are providing services within VA in increasing numbers over the past 13 years, as with any new service, adoption and appropriate placement faces challenges. Many VA providers may know little about the clinical approaches used by DCs.[29] Similarly, DCs may not be fully aware of the processes involved in the delivery of primary care services within VA or the healthcare needs of veterans with mental illness.[30] Consistent with the intent of the R34 mechanism, this pilot study will not include formal tests of outcomes, but will collect preliminary data regarding the feasibility, perceptions, safety, tolerability, and target outcomes relevant to planning future RCTs. **Thus, the purpose of this pilot clinical trial is to evaluate the feasibility, safety and patient perceptions of an integrative care pathway, developed through a consensus-based process, for the coordinated care for VA patients with cLBP and mental health comorbidity.**

3. STUDY DESIGN

This pilot study is a single-arm clinical trial of 40 veterans aged 18 and older, who have cLBP from the ICVAHCS and the Coralville, Iowa Community-Based Outpatient Clinic (C-CBOC), also a VA setting. Participants will receive up to 10 weeks of chiropractic care, including but not limited to SMT, mobilization, active exercises, and self-care recommendations. **See Appendix A for Study Flow.** We will recruit 40 veterans with cLBP with or without a mental health comorbidity such as anxiety, depression and/or PTSD. Participants will receive co-managed care by a collaborative care team that includes a primary care provider, DC, and/or mental health professional, as the individual's health status warrants.

The primary patient-reported outcome is LBP-related disability as measured by the Roland Morris Disability Questionnaire (RMDQ) and the Brief Pain Inventory (BPI). Secondary patient-reported outcomes include PHQ-9, GAD-7, PLC-C, AUDIT, STarT Back, self-efficacy for managing symptoms (SF8a), self-care behaviors, EXPECT, HEAL, and PEG questionnaires, and the PASTOR assessment, which includes measures of LBP intensity and interference as measured by the DVPRS, pain, disability, mental health, quality of life enjoyment and satisfaction. Outcomes will be collected at BV and at 3, 5, 7, and 10 weeks. Outcomes will be obtained by participant self-report through web-based direct-entry using REDCap (Research Electronic Data Capture). We will also evaluate health service use, including the number of visits to the DC, as well as primary care, mental health, and other providers, and medication use using electronic health record (EHR) through EHR extraction.

The Palmer Center for Chiropractic Research (PCCR) will take responsibility for all aspects of project management, data collection and management, and statistical analyses. The Yale Center for Medical Informatics will be responsible for extracting EHR data on participant demographics and health service use. The ICVAHCS will be responsible for developing EHR-data extraction methods for recruitment purposes, providing DCs with mental health training, and will assist in participant recruitment. The

ICVAHCS will also be responsible for assisting veterans with setting up the online patient portal access. Licensed DCs at the ICVAHCS will provide the chiropractic care.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Individuals interested in participating in this pilot study must meet all of the following inclusion criteria:

- Veterans age 18 years or older
- Self-reported chronic LBP
- Ability to comprehend study details
- For 75% of the study population: one or more mental health conditions defined as depression, anxiety, or post-traumatic stress disorder

4.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation. Exclusion criteria are:

- Use of chiropractic care within the past 90 days
- Impaired cognitive ability
- Not a candidate for chiropractic care
- Not able to attend chiropractic appointments
- Potential suicide risk
- Unable to complete questionnaires without help from a proxy

Table 1. Eligibility Criteria		
	Deciding Study Team Member	**Rationale**
Inclusion Criteria		
1.Veterans age 18 and older	Project Manager	Study population
2.Self-reported cLBP: persisted 3 or more months and pain on at least half the days in the past 6 months	Project Manager	Study population, standardized definition
3.Able to comprehend study details	Project Manager	Able to comprehend study details and make decisions without limitations or impairment
4.For 75% of the study population: one or more mental health conditions defined as depression, anxiety, or post-traumatic stress disorder	Project Manager	Study population
Exclusion Criteria		
1. Received any chiropractic care outside VA or any VA related chiropractic services within past 90 days.	Project Manager	prevent potential carryover effects
2. Impaired cognitive ability such that a potential participant is unable to provide fully informed consent,	Project Manager	Prohibits informed consent

including those with a legally authorized representative or guardian who renders medical decisions for them.		
3. Not a candidate for chiropractic care due to contraindication (e.g., inflammatory spondyloarthropathy, surgical intervention needed, recent spinal/pelvic fracture) or other clinical factors.	DC	Not a candidate for chiropractic care as a management strategy for chronic LBP
4. Not able to attend chiropractic appointments per recommended chiropractic treatment plan.	Project Manager	Study compliance
5. Active suicide monitoring flag listed in EHR as high or moderate risk, or individuals who report active suicidal ideation to the DC, primary care, or mental health provider within 30 days of BV.	Project Manager, DC, PC, or MH	Suicide risk
6. Not able to complete questionnaires without the help of a proxy.	Project Manager	

Definition of Chronic LBP: We define chronic LBP consistent with the NIH task force on Research Standards.[31] Individuals who report LBP as an ongoing problem for more than 3 months and who also report LBP as an ongoing problem during at least half the days in the past 6 months will be classified as meeting the criteria for chronic LBP.

Definition of Mental Health Condition: For the purposes of this pilot study, we are limiting mental health conditions to anxiety, depression, and/or PTSD. Patients will be considered eligible if they have a current diagnosis of one of these 3 mental health conditions as determined by a clinician guided review of their medical records. The conditions must be identified in a problem list and the medical records should reflect a provider of record who is actively managing the condition. A list of potential subjects will also be identified by screening the EHR for veterans with low back pain and the three identified comorbid mental health conditions by using ICD-9/10 codes using published methods.[32] Participants with these mental health comorbidity will have active management (within last 90 days) evidenced by primary care or mental health provider documentation. Patients will also be considered classified for having one of the stated mental health conditions if they meet a minimum cut-point score on any of the following 3 measures. Cut-points are a score of 10 on either the PHQ-9 or GAD-7 or a score of 31 on the PCL-C. The PHQ-9 and GAD-7 instruments are standard measures to screen for depression and anxiety. Cut-points were determined by the site PI who is specialty certified in mental health and they are consistent with values recommended in relevant literature.[89-92]

Veterans with suicidal ideation are not eligible for the study. However, patients may develop suicidal ideation during the course of the study. These symptoms will be recorded via the online symptom database (PHQ-9). Should the patient indicate in question 9 “Thoughts that you would be better off dead or of hurting yourself in some way” with any response other than “not at all”, REDCap will flag the response and immediately send a notification to the PM. In the event this occurs, the PM will immediately alert the treating provider and the study site PI (Dr. Abrams) of the suicidal ideation. The treating provider will contact and manage patient care and the site PI will be alerted but remain independent of this management. Only in cases where the provider is unable to be contacted or the psychiatrist of the day (POD) is unreachable will the site PI (Dr. Abrams) be contacted for management. For all patients, emergency contact names will be collected so study personnel may enlist additional help to ensure

veteran safety and evaluate the need for more specialized care. Regular contact will occur between the referring providers and the site PI via conferences and normal clinical collaboration within the Primary Care Mental Health Integration (PCMHI) model.
In addition, VA provider staff are trained in specific protocols to address issues related to worsening of depression and risk for self-harm **(See Appendix B Suicide Risk Protocol).**

4.3 Study Enrollment Procedures

Recruitment: One feasibility aim of this pilot study is to test our recruitment and retention strategies. We plan to enroll 40 participants to test the utility of the integrative care pathway for veterans. An additional goal is to test our ability to recruit women and ethnic/racial minorities for a larger trial. We will work with the VA Women's Health Practice-Based Research Network toward this goal. Avenues to be tested include oversampling these groups in samples identified through the EHR, targeting women's healthcare clinics as part of our overall recruitment strategy, and creating flyers and other study recruitment materials that are inclusive.

Our *a priori* approach is to recruit participants through a 3-pronged recruitment strategy: 1) invite potential participants to be screened for the study using EHR, 2) referral through the existing models of care, or 3) standard direct recruitment procedures. We will modify recruitment strategies as needed and with IRB-approval should the following methods be found insufficient to reach our enrollment targets.

1) **Strategy 1: Letter invitation for screening using EHR**
   VA Corporate Data Warehouse (CDW) will be used to conduct the EHR pre-screening protocol. Each patient record has unique identifiers comprised of formula-based encryptions of the individual's Social Security Number (SSN). The identifier for a given patient is consistent across datasets and fiscal years. Access to files that translate scrambled to real SSNs is possible with special authorization, which will be obtained through an IRB-approved process granted by the Data Acquisition and Request Tracking system.

   Data files will identify potential participants for initial contact via recruitment letter on ICVAHS patients with a visit to a primary care provider with a low back pain ICD-10 code **(See Appendices C-D. ICD-9/10 Diagnosis List)**. We will extract patient identifiable data to allow us to contact potential participants, including full name, address, age, sex, race, ethnicity, service connected %. We will use the patient gender and race/ethnicity to evaluate processes for recruitment of women and minorities into the study. This step using the pre-screen EHR database is necessary to determine participants initially eligible for contact regarding the study. Service connection percentage will be used to describe the study sample in scientific presentations and publications. Because one goal of this study is to ensure women and minorities are included, gender and race/ethnicity status data will inform recruitment strategy decisions for a follow-up trial.

Veterans identified as potential participants will receive an IRB-approved template letter printed on VA letterhead explaining: 1) they were identified through the use of routinely collected clinical data captured as part of their VA care; 2) the basic parameters of their potential study eligibility; 3) the study objectives; 4) anticipated treatments performed by the DC, which would be considered usual chiropractic care; and 5) a request that they call a dedicated line at the Palmer research center or complete a postcard that accompanies the letter and mail it back to the study team. The dedicated phone line is only for research participants. It is what we have used in our previous studies. This is not answered live, but requests that callers leave contact information. The PM/study coordinator and back-up study coordinators are the only members of the study team to gather this information, put the contact information in REDCap and then delete from the voicemail. This will help limit too many calls coming to the PM study cell phone for simple inquiries on the study. The postcard contains simple boxes asking additional eligibility questions and willingness to participate in the research study. If a potential study participant fails to return the postcard or call the research line, the PM will call, confirm receipt of the letter, and ask them to send in the postcard or ask if they are interested in the study. Following confirmation of initial eligibility, the PM will advise potential participants on next steps for study consideration.

2) **Strategy 2: Developing and testing of research engagement using existing patient flow through existing models of care**
Congruent with the VA model of delivering care, veterans are assigned a Patient Aligned Care Team (PACT) for primary care services and coordination of other referrals. Providers will incorporate a brief screening procedure into the routine clinic assessments to identify veterans who may be eligible for study participation. Clinic personnel will review patient records on key inclusion criteria, including back pain location and duration and current mental health diagnosis, and query patients about their interest in learning more about a study of chiropractic care for LBP. If the patient indicates a willingness to learn more about the study, recruitment materials will be delivered by clinic personnel at the point of care to facilitate patient referral from the PACT to the study PM. Included in this strategy is recruitment directly from the chiropractic schedule for patients who have already been referred by their PCP to see a chiropractor for cLBP but have not heard of the study yet. Additionally, we will develop and test EHR-embedded consult templates for referral to the study.

3) **Strategy 3: Standard direct recruitment procedures**
We will recruit VA patients directly using informational items describing the study, including contact information, in coordination with the local VA research office. Examples of such items are brochures, flyers, and pens. Distribution will be focused on the chiropractic clinics themselves, targeting patients who have not seen the DC in the prior 3 months, as well as areas where the highest volume of primary care patients are encountered and at IRB-approved outreach events. We will also conduct provider and staff in-service educational sessions, visits to local community-based outpatient clinics (CBOCs), and local veteran socialization and care centers (e.g., Veterans of Foreign Wars (VFW), Vet Centers). Interested veterans recruited through these methods will be asked to call the PM for additional information about the study.

Enrollment: Another feasibility aim is to determine the rate of enrollment into the clinical trial. We anticipate enrollment to occur at the rate of **6-8 participants per month** over a period of 6 months.

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The PM will screen interested veterans on objective eligibility criteria using a telephone interview **(See Appendix G Phone Screen)**. The PM will confirm initial eligibility and advise potential participants on next steps for study consideration. Potential participants who had been seen in VA chiropractic clinics within the past 2 years and meet other inclusion/exclusion criteria (those who have been to the DC in the past 90 days are not eligible) will be advised to contact the given chiropractic clinic directly to schedule a baseline assessment, consistent with VA policy. All other potential participants will be advised to contact their primary care provider for a referral to the chiropractic clinic. Baseline study visits will include the informed consent process **(See Appendix H Informed Consent Document)**, and a screening interview with the PM **(See Appendix I Baseline Screening)**. After signing the informed consent document and completing the BV, the PM will perform a final screen to confirm eligibility, with an emphasis on ensuring that the Veteran has not had any of the suicide risk factors listed in Table 1. The appropriate clinical evaluation by a VA DC **(See Appendix J Chiropractor Screening)** will occur at the initial chiropractic visit. Following the chiropractic evaluation, eligible participants still meeting eligibility criteria (Table 1) will be formally enrolled into the trial by the PM. For those not meeting trial criteria, data on the reasons for ineligibility will be recorded. Ineligible participants will receive routine care in the chiropractic clinic and/or be referred for other LBP treatment consistent with VA management practices.

Retention: Participant retention strategies include frequent contact via MyHealtheVet (for those with internet and a computer), convenient scheduling of chiropractic visits with take-home appointment calendars, reminders of upcoming visits at each session, day-before reminder calls, follow-up calls, and rescheduling of missed appointments. This method of contact is for clinical appointments at the VA and monitored by VA clinic offices.

Participants also will complete outcome assessments online. Participants will have a one week window of time to complete electronic assessments. The Data Core Manager and PM will monitor compliance and provide additional reminders to participants to complete assessments as necessary. An automated email reminder to complete assessment will be sent to participants via REDCap the day the assessment window opens, and the day the assessment is actually due. The PM will make personal contact via texts/calls at least once in an attempt to remind the participant to complete the assessments during the active assessment window. Once the active window closes for weeks 5 and 10, the PM will contact participants that did not respond to try and complete a Computer Assisted Telephone Interview (CATI). Up to three attempts will be made within 7 days following window close date.

Incentives, Compensation and Travel Reimbursement

1) **Incentives:** To increase awareness of the COCOV Trial, VA staff and potential participants will be given small novelty items such as pens or keychains that contain research study contact information, free-of-charge throughout the recruitment period. Upon enrollment, participants will receive a wallet-sized plastic card listing study contact information to facilitate communication with study staff. This concept was a successful retention tool in a previous study focused on recruitment of veterans.[33]

2) **Compensation:** Participants will be compensated for their time spent in the completion of study data collection procedures. Participants will receive a $25 gift card after completing assessments at BV, Week 5 and Week 10. Upon completion of all study assessments, an additional $25 gift card will be given, for a potential total of $100 in study compensation.
3) **Travel Reimbursement:**
The research team will make an effort to arrange research data collection coinciding with existing healthcare visits when possible. However, when research visits, the baseline visit and exit interview, are required for data collection outside existing clinical appointments the Veteran will be reimbursed using the following procedures. Travel payments will be made at .56$ per mile for distances beyond 20 miles. The veteran's social security number and address will be confirmed and a check will be mailed for their travel from the Palmer Center for Chiropractic Research.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

1) **Interventions:** As this pilot study is a trial, chiropractic care will consist of usual chiropractic procedures for the management cLBP. Treatment approaches will be based on a clinical evaluation, which may include diagnostic testing, to determine a working diagnosis, rule out pathology, and/or to screen for conditions requiring referral or other co-management. We anticipate that chiropractic care often will include some form of SMT or mobilization to address the patient's specific needs. DCs will recommend other interventions such as rehabilitative exercise, stretching, or nutritional and lifestyle advice based upon clinical findings and patient goals/preferences. We will monitor treatments provided through EHR chart abstractions conducted following completion of chiropractic care at Week 10.

   As per typical VA care, DCs will monitor the participant's health status throughout the trial and initiate referrals as clinically indicated. Referrals to primary care and mental health providers will be consistent with the chiropractic integrated care pathway developed during Phase 2 of the COCOV study **(See Appendix K Integrated Care Pathway)**. We anticipate the most common communication and referral methods will occur through note-review and countersign procedures, which are already established among VA providers using the VA electronic health record, but may also occur in person or via phone conversations.

2) **Administration of Chiropractic Care:** Chiropractic care will be administered by licensed DCs who are current employees of the ICVAHCS.

3) **Intervention Duration/Dose:** Participants will receive chiropractic care at a frequency of 1-2 visits per week for a duration up to 10 weeks, with the frequency and duration of care individualized within established VA parameters and per the COCOV chiropractic integrated care pathway **(See Appendix K)**. For this trial, the minimum treatment dose is 1 visit to the DC, while the maximum treatment dose is 12 visits to the DC.

5.2 Handling of Study Interventions

Study participants will be expected to follow care recommendations given to them by

their health care providers, including visit frequency, as well as complete study assessments at the indicated times during their study participation.

5.3 Concomitant Interventions

Data regarding participant care for cLBP that is delivered within VA will be obtained from VA EHR. In addition, participants will be asked to describe any care they received for the cLBP outside of VA system, including use of complementary therapies and self-care. The following is a list of allowed, required and prohibited interventions in this trial.

5.3.1 Usual Medical Care

Participants will have access to the same usual medical care available to all veterans during the study timeframe. Usual care will be defined as any care designated by the PACT provider of record. In most cases this will be a combination of treatments or referrals that could consist of 1) systemic medications (e.g., nonsteroidal anti-inflammatory drugs (NSAIDS)), 2) topical therapies (e.g., creams), 3) low intervention transcutaneous treatments (transcutaneous electrical nerve stimulation (TENS), ultrasound, trigger point injections), 4) supportive braces; and 5) referrals to physical therapy or specialty care for invasive procedures such as nerve blocks or spinal injections.

5.3.2 Required Interventions

The chiropractic care provided by study DCs will be a structured approach to typical evidence-based, combination care management of patients with cLBP as commonly delivered in VA and as described above. This will include standard diagnostic elements such as review of medical records, patient history and physical examination, and additional diagnostic testing if indicated. In shared decision-making with participants, the DCs will develop an individualized treatment plan including patient education on chronic pain, patient instruction/engagement in active strategies such as therapeutic exercise, body mechanics/ergonomics, and self-management advice. Manual treatment will include SMT and/or mobilization, and/or massage/myofascial therapies. DCs will engage in routine collaborative communication with other providers as indicated. **In order to provide an approach that is generalizable yet still allows pragmatic decision making at the clinician level, we will use a patient care pathway** based upon algorithms that the investigators have previously developed through a Delphi process. Examples of manual therapies that may be delivered to participants (based upon the treatments currently used by DCs at ICVHCS) include the following:

SMT to the low back region will be most commonly performed with the patient in a side-lying position and the free hip and knee bent. The DC will contact the patient's bent lower extremity with his/her own thigh to stabilize the lower body. With one hand, the DC will stabilize the patient's free shoulder or upper arm. With the other hand, the DC will apply a high-velocity, low amplitude manual thrust toward a lumbar or sacroiliac joint complex. This procedure often results in local joint gapping referred to as cavitation.[34]

Manually held instruments, such as an Activator (Activator Methods International LTD,

Phoenix AZ) may also be employed. These instruments are hand-held spring-loaded devices that deliver a quick impulse, or thrust, of several millimeters to a target vertebrae or joint.[35] Hand-held mechanical devices are often used when manually delivered interventions are not well-tolerated or otherwise preferred by patients.

Trigger point therapy consists of manually applying pressure to abnormally taut areas within muscles.[36;37] These are tender areas that sometimes refer pain to remote areas.[38;39] Pressure is applied for several seconds within patient tolerance to break a self-perpetuating cycle causing pain, hypertonicity, and inflammation in a muscle. Increased circulation following pressure removal is thought to help remove inflammation within the muscle region.

Gua sha is characterized by applying friction (or scraping = Gua) to a body region using an instrument such as a coin or spoon.[40] The result being a bruising effect (sha) noticeable on the skin of the area treated. Some evidence suggests that Gua sha improves microcirculation in surface tissues and modulates anti-inflammatory activity within the body, thus contributing to reduced pain often reported following treatment.[41]

5.3.3 Prohibited Interventions

It is not our intent to expressly prohibit any interventions during participation in the trial. However, we will ask providers and patients to avoid acupuncture during the active treatment phase of the study. While acupuncture is available through the ICVAHCS chiropractic clinic, the delivery of this intervention would serve as a confounder to the chiropractic intervention given this pilot trial's small sample size.

5.4 Feasibility Assessment

For this pilot trial, feasibility measures will focus on the extent to which participants complete their scheduled assessments and complete all scheduled treatment visits to the DC. **See feasibility measures in Appendix L and M, Feasibility Outcomes and Feasibility Metrics**.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Phone Screen:	Baseline Visit	Initial DC Visit	Week 3	Week 5	Week 7	Week 10	EHR
Demographics	X*							X
Confirm Eligibility Criteria	X*	X	X					X
Informed Consent		X						
Medication & Medical Hx								X
Chiropractic Examination			X					
Enrollment			X					
RMDQ (back disability)		X			X		X	
Brief Pain Inventory		X			X		X	
PHQ-9 (depression)		X					X	
GAD-7 (anxiety)		X					X	
PLC-C (PTSD)		X					X	
AUDIT (alcohol)		X					X	
PASTOR								
DVPRS (pain/QOL)			X[1]		X		X	
Pain Questions			X[1]		X		X	
Body Diagram			X[1]		X		X	
PROMIS Global Health			X[1]		X		X	
PROMIS Neuro Pain			X[1]		X		X	
PROMIS Pain Int.			X[1]		X		X	
PROMIS Phys Funct			X[1]		X		X	
PROMIS Fatigue			X[1]		X		X	
PROMIS Sleep			X[1]		X		X	
PROMIS Depression			X[1]		X		X	
PROMIS Anxiety			X[1]		X		X	
PROMIS Emot Dist			X[1]		X		X	
PROMIS Satisfaction			X[1]		X		X	
PROMIS Alcohol			X[1]		X		X	
TBI QOL Headache			X[1]		X		X	
PTSD Screen			X[1]		X		X	
Opioid Use			X[1]		X		X	
Treatment History			X[1]		X		X	
Pain Medication			X[1]		X		X	
Alignment to Treatment			X[1]		X		X	
STarT Back			X[1]				X	
SF8a (self-efficacy)			X[1]				X	
Back Pain Activities			X[1]				X	
EXPECT (expectations)			X[1]					
HEAL (non-specific effect)			X[2]				X[3]	
PEG (pain and activity)				X		X		

Adverse Events					X		X	
Qualitative Exit Interview							X	

[1] Measure completed before first treatment.
[2] Measure completed after first treatment.
[3] Measure completed before final visit.
*** Items will be asked of Veterans and confirmed with EHR screening**

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

Informed consent will be obtained in 2 stages. First, veterans interested in participating in this pilot study will be asked for a verbal consent to answer initial phone screen questions. If a veteran meets initial study eligibility, a second written informed consent will be obtained by the project manager, who will be the primary study coordinator, when the veteran arrives at BV. The PM will review the informed consent documents with the veteran and allow for any questions before the veteran voluntarily signs the consent document and HIPAA forms. Current informed consent documents will be monitored for correct IRB approval dates and maintained according to IRB standards. When the PM is not available, a back-up study coordinator will complete phone screens and consent potential participants.

Electronic Health Record (EHR) Data Extraction

EHR data will be utilized to provide initial screening information and to confirm eligibility criteria. Items collected from the EHR include age, and contact information.

Screening

Upon initial interest, veterans will contact the PM for a phone screen to determine initial eligibility. After obtaining verbal consent, the phone screen will consist of age and medical history pertaining to study eligibility.

If the veteran meets preliminary eligibility, he or she will be invited to attend a BV. Because participants must also be eligible for chiropractic care, an initial chiropractic visit must also be scheduled. The BV will not be scheduled until the initial chiropractic visit is scheduled.

The BV will be scheduled up to 10 days before or on the day of the initial chiropractic visit, depending on schedule availability. At the BV, veterans will provide written informed consent. Upon signing the informed consent document, veterans will complete study contact information (preferred address, phone, and emergency contacts) and review final eligibility criteria. Enrollment will be completed upon chiropractic examination, which determines the final eligibility criterion.

6.2.2 Enrollment and Outcome Assessments

Enrollment

Participants will be enrolled into the study after completing an examination performed by the DC at the Initial Chiropractic Visit and the PM has reviewed all forms to confirm completeness and eligibility. This date will be recorded by the PM as the enrollment date. All assessments in the study will use the enrollment date at the initial treatment date.

Patient-reported Outcome Measures and Other Assessments

Patient-reported outcomes will be obtained by participant self-report through REDCap a secure web-based direct-entry application; the schedule of data collection is shown above. The assessments at baseline and weeks 3, 5, 7 and 10 will be collected through REDCap with the primary endpoint at 10 weeks from enrollment. During the BV the PM will use a password protected, limited access, laptop owned by Palmer College of Chiropractic. The information transmitted will be encrypted and no data will be stored on the laptop. Baseline interview is completed by reading questions to a participant and entering verbal responses to the web form. If the participant is eligible after the baseline interview, the PM will log out and instruct participant on how to access REDCap to complete the first set of BV questionnaires, and participants will receive email invitations which includes a link to their REDCap questionnaires for each remaining time point, to be completed on their own device. If a participant cannot complete the questionnaires online at any time-point, they may complete them by CATI with the PM. The PM will read the questions aloud and enter the verbal responses directly into REDCap. CATIs for or week 5 and week 10 will only include the Roland Morris Disability Questionnaire and the Brief Pain Inventory. Each data collection instrument is described below and included in **Appendix N, Study Assessments.**

- **Roland Morris Disability Questionnaire (RMDQ**). As in our previous LPB studies[42-46], we will use the patient self-report modified 24-item version of the RMDQ to assess LBP related disability. The RMDQ may be the most common and respected assessment instrument in LBP outcomes research. It is a one-page questionnaire related to low back pain disability with documented reliability and validity.[47] The RMDQ can discriminate between different forms of treatment for back pain, and is sensitive to clinical change. The RMDQ has been chosen for a number of clinical trials of LBP treatments for its excellent metric properties, ease of use, patient acceptance, and high face validity.

- **Brief Pain Inventory (BPI) – Short Form:** This self-reported instrument will be used to assess pain intensity and pain interference. The BPI was developed to assess the pain associated with cancer, but is now used for many types of pain.[89-90] The scored items of the survey includes 4 questions to rate pain intensity using a 0-10 numeric rating scale (NRS). The final 7 questions use a 0-10 NRS to rate how pain interferes with activities of daily life, mood, relationships, sleep and enjoyment of life.

- **Patient Health Questionnaire (PHQ-9):** This instrument is self-reported with nine items and will be used to assess depressive disorder.[52;53] Total scores range from 0 to 27 with a score of 10-14 considered to be in the moderate range. It has been tested in primary care settings and has a test-retest reliability of 0.81 to 0.96. Per VA practice, this instrument is delivered by primary care providers annually.

- **Generalized Anxiety Disorder-7 (GAD-7):** This instrument is self-reported with seven items and will be used to assess generalized anxiety disorder.[52;54] At a cut off score of 10, it has a sensitivity of 0.89 and specificity of 0.82 for identifying patients with GAD in primary care settings. Per VA practice, this instrument is delivered by primary care providers annually.

- **PTSD Checklist-Civilian (PCL-C):** This 17-item, self-reported instrument will assess PTSD.[56-58] A total severity score is determined by summing scores from each of 17 items. A change of 5-10 points represents the minimum threshold for determining treatment response; a 10-20 point change represents a clinically significant change in PTSD symptom severity. This instrument is given annually in the VA following OEF/OIF (Operation Enduring Freedom/Operation Iraqi Freedom) deployment return, then every five years after that.

  Note: PHQ-9, GAD-7, and PCL-C are measures used at the ICVAHCS as the current standard of care.

- **Alcohol Use Disorders Identification Test (AUDIT):** Developed by the World Health Organization (WHO), this 10-item screening questionnaire determines harmful or hazardous consumption of alcohol, correctly classifying 95% of people as having a clinical diagnosis of an alcohol abuse disorder.[55] Per VA practice, this instrument is delivered by primary care providers annually.

- **Pain Assessment Screening Tool and Outcomes Registry (PASTOR):** PASTOR is a comprehensive, on-line, data collection tool for chronic pain based upon the NIH Patient Reported Outcomes Measurement Information System (PROMIS) and adopted by the DoD/VA Pain Management Task Force. PASTOR contains many of the domains recommended by the NIH Task Force recommendations[31] for a minimum dataset for cLBP. Specific measures include the Defense & Veterans Pain Rating Scale (DVPRS), an enhanced 11-item (0-10) numeric rating scale (NRS) that improves on standard pain NRS by including a Faces Rating Scale component; 'traffic light' color-coding system to delineate mild, moderate and severe pain; and word descriptors indicating pain perceptual experiences and functional limitations from the painful episode, paired with 4, 0-11 NRS items to quantify the impact of pain on general activity, sleep, mood, and stress. PASTOR incorporates PROMIS measures for mental health conditions (PTSD, depression, anxiety, anger, and alcohol use), physical and social function, fatigue, and pain interference with daily activities to provide graphical representation of improvements or declines in patient status that are compared to matched US samples on age, race/ethnicity and sex. PASTOR is the ideal instrument for accomplishing the parallel goals and functions to "implement and effectively use health information technology" and "innovate and strengthen methods for researchers to improve measurement of patient-centered outcomes of treatments and other interventions for individuals with multiple chronic conditions."[48] It provides a 3-page Clinician Report with information on pain treatment history and current opioid use and PASTOR takes 20-30 minutes to self-administer, and can be completed off-station to fit the Veterans' work/home schedule. Psychometric testing of the DVPRS 2.0 in 307 active duty service members and Veterans with acute or chronic pain reported acceptable internal consistency reliability and test-retest reliability on the 5-items, with excellent inter-rater reliability for correctly ordering the pain faces with intensity measures, and highly rated superiority of the instrument again other pain rating scales.[49] DVPRS was significantly correlated with the Pain Disability Questionnaire, Veterans RAND-36, and Brief Pain Inventory in VA outpatients.[50]

- **STarT Back Screening Tool:** This is a 9-item, validated tool developed by Keele University to be used as a screening tool for patients with low back pain[51]. It stratifies patients based on their prognosis of persistent disabling symptoms and allows practitioners to group patients into 3 categories (low, medium, or high risk of poor outcome).

- **Self-Efficacy for Managing Symptoms (SF8a):** Developed by PROMIS, this 8-item, self-reported tool will assess a person's level of confidence to control their symptoms and keep them from interfering with activities.

- **Back Pain Activities:** These assess self-care strategies were developed from previous studies that collected patient-reported self-care activities[59;60] utilized at baseline and week 10.

- **EXPECT (Expectations for Complementary and Alternative Medicine Treatments):** This questionnaire was developed to assess individuals' expectations of treatments for chronic pain.[61]

- **Healing Encounters and Attitudes Lists (HEAL):** HEAL is a validated item-bank comprised of 6 domains developed through PROMIS methodology.[62] We will use HEAL to assess nonspecific factors known to influence patient outcomes, including perceptions of the doctor-patient relationship,[63-69] treatment expectancy,[70;71] and positive or negative outlook.[72] HEAL will be administered after the Initial Chiropractic Visit and during the week before the Week 10 assessment period.

- **Pain, Enjoyment, and General Activity (PEG):** The PEG is a 3-item tool to improve assessment and monitoring of chronic pain. Questions assess average pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G).[73] In future clinical trials, PEG questions will be collected via SMS text messaging, which is beyond the scope of this pilot trial. However, this will provide the study team with experience using this instrument and is being collected at Week 3 and Week 7 to offset the other outcome measures collected at Week 5 and Week 10.

- **Qualitative Exit Interviews:** We will conduct a process evaluation using a mixed methods approach to assess non-specific treatment factors and stakeholder experiences with the study interventions to better understand how site-specific variations influence the implementation of chronic pain interventions. Qualitative interviews at Week 10 will evaluate how Veterans and clinicians experienced the study interventions, assess their perceptions of non-specific treatment effects, and gather recommendations for implementation of these services across VA settings. The interview will be scheduled at weeks 8-10 of the study or up to two months after week 10, depending on when we are able to contact the participant. The PM, Dr. Stacie Salsbury (Co-I), or the assistant study coordinator will conduct the individual, semi-structured interviews with participants either in person or by phone, depending on the participants preferance. **Questions are in Appendix O Exit Interview Questions**. Providers will also be invited to

complete an exit interview after all participants have completed their study activities. Dr. Salsbury will train the PM and the assistant study coordinator in a standardized interview schedule and interview best practices and provide annual/as needed re-trainings to assure adherence to interview protocols. The interview schedule will include a section with the identical questions for all participants to elicit perceptions of treatment factors and healthcare setting which will be modeled upon items from the HEAL instrument. Interviews will be digitally audio-recorded, last about 15 minutes in duration, professionally transcribed, and assessed for data quality before data analysis.

Compliance, Co-interventions, and Attrition:
During the course of the study, feasibility metrics will be monitored by the PM and the research team. These metrics include processes relating to recruitment, informed consent, trial enrollment, treatment scheduling, retention, and communication. Protocol quality measures, EHR data extraction, and adequacy of outcome measures will also be recorded. **See Appendix L, Feasibility Outcomes and Appendix M, Feasibility Metrics.**

Randomization

As this is a single-arm trial, no randomization occurs during this pilot study.

6.2.3 Blinding

No blinding of participants occurs during this trial. All health care providers, co-investigators, and the PM will be blinded to study outcome measures.

6.2.4 Follow-up Visits

Because of the pragmatic nature of this pilot study, participants will be scheduled for follow-up visits as indicated by their provider. Study assessments will take place independently of care visits, but will coincide with weeks of care since study enrollment. The following assessments will be collected at the indicated times during study participation online. Participants will have a window of one week to complete each assessment.

6.2.5 Completion/Final Evaluation

Upon completion of the week 10 assessments, the PM will contact the participant to complete the qualitative exit interview, as described above.

7. SAFETY ASSESSMENTS

Chiropractic care includes manually applied therapies including active and passive exercise, friction and non-friction based myofascial therapies, and non-thrust joint and thrust joint manipulation.

Adverse events from chiropractic care are common and similar to those experienced by patients undergoing other manual therapies such as physical therapy or massage. Adverse events are usually mild, short lasting, and self-resolving musculoskeletal

symptoms such as stiffness, joint or muscle soreness, and increased or radiating pain in the region treated.[74] Many adverse events associated with chiropractic care are likely not caused by interventions; rather, by normal variations in symptoms inherent to musculoskeletal conditions such as neck and back pain.[74] Less commonly reported adverse events include dizziness, nausea, tinnitus, anxiety, and muscle spasm.[75,76] Serious adverse events associated with chiropractic care are extremely rare. Serious adverse events associated with chiropractic care for low back pain are so uncommon that population-based risk ratios are unknown.[77]

High-velocity spinal manipulation to the cervical spine has been hypothesized to increase risk for vertebral artery dissection and stroke due to excessive carotid or vertebral artery stretching/kinking. However, cervical spine manipulation results in less stretch/strain to the major neck arteries than what occurs during normal range of motion.[78;79] Several epidemiological studies have consistently shown an equivalent, extremely low, risk of suffering a cerebrovascular accident whether or not patients visit a primary care practitioner or doctor of chiropractic.[80-85] This research strongly suggests patients who experience cerebrovascular accidents following chiropractic care most likely experience events despite, rather than because of, an intervention.[86]

7.1 Specification of Safety Parameters

DCs are trained to avoid or modify therapies for patients who exhibit a relative or absolute contraindication. An examination will be performed by the DC as part of the eligibility determination process. Clinical evaluation will also occurring during each chiropractic visit before treatment is delivered. The eligibility exam is designed to identify participants with a suspected or confirmed condition that prevents the safe delivery of chiropractic care, the need for referral or diagnostic testing. Individuals identified with these factors during eligibility examination will be excluded from participation until such a time when the comorbid condition, diagnostic evaluation, or alternate treatment is resolved or no longer necessary.

As outlined in the Data Safety and Monitoring Plan below, an independent Data and Safety Monitoring Committee (DSMC) will provide scientific and ethical oversight for the clinical trial.

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

We will inquire about adverse events at weeks 5 and 10 using a questionnaire asking "Did you experience any discomfort or unpleasant reaction after any of your chiropractic treatments?" "Yes" responses will be followed by indicating a category (e.g., increased pain, stiffness, muscle weakness, headache). Severity of symptoms will be rated by checking one of the following categorical responses: Symptoms did NOT require changing or modifying regular activities; Symptoms required modifying regular activities or for which treatment is needed; Symptoms required bed rest, lost work, or prevented you from regular activities; Life-threatening or required in-patient hospitalization (please explain). Duration of symptoms will also be recorded (less than 24 hrs; 24-48 hrs; 48hrs-1 week; 1-4 weeks; >4 weeks).

Participants will also be instructed to contact study staff if they experience a change in health status or significant pain, discomfort or distress regardless of whether or not they believe it may be associated with treatment including after final treatment. Participants

are also asked to inform the PM of any unplanned emergency room or hospitalizations for either LBP or mental health issues.

7.3 Adverse Events and Serious Adverse Events

We will define an adverse event (AE) as any untoward health occurrence that may present itself during the clinical trial and that may or may not have a causal relationship with chiropractic care. We will use the FDA definition of serious adverse event (SAE), which is any adverse experience occurring during treatment that results in any of the following outcomes: death, a life-threatening adverse experience, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Unanticipated Problems Involving Risk to Subjects or Others (UPIRSOs) are similar in that they are unexpected, related or possibly related to participation in the research and may involve a greater risk of harm. Events not meeting the criteria for immediate reporting will be submitted to the IRBs in summary format during the annual continuing review. All SAEs and UPIRSOs will be reported according to VA and/or IRB requirements.

7.4 Reporting Procedures

Adverse events meeting IRB reporting criteria will be communicated to each respective IRB. Additionally, all adverse events that may have an effect on the safety or rights of study volunteers will be reported to the DSMC as required. Events not meeting the criteria for immediate reporting will be submitted to the IRBs in summary format during the annual continuing review. All SAEs and UPIRTSOs will be reported according to VA and/or IRB requirements.

7.5 Follow-up for Adverse Events

The PM will follow-up by phone when participant answers indicate “symptoms were life-threatening or required in-patient hospitalization” on the questionnaire **(Appendix P)** inquiring about discomfort or unpleasant reactions from treatment. The PM will also follow-up by phone with any participants that reported any hospital admission or ER visit for LBP or mental health conditions. The PM will collect information regarding AE’s. The senior clinician will grade each event and report as necessary.

7.6 Safety Monitoring

An NIH/NCCIH approved DSMC will consist of individuals independent of the participating sites. Members will have expertise in chiropractic, medicine, psychiatry, epidemiology, clinical trials and biostatistics. The DSMC will meet at least twice per year either in person or by teleconference. The DSMC will approve the pilot study protocol, informed consent document, and human research participant protection procedures before trial implementation. To monitor trial data, the DSMC will review status reports prepared by the trial biostatistician that include recruitment accrual; enrolled participant baseline characteristics and other enrollment data; follow-up assessment completion; treatment compliance; protocol deviations and other clinical trial data. To monitor participant safety, the DSMC will review reportable adverse events every six months and will assess any serious adverse events upon report receipt. This pilot study will have an annual Research Compliance Officer (RCO) review.

8. INTERVENTION DISCONTINUATION

Given the nature of the intervention under study, no formal stopping rules will be used. The DSMC will make recommendations to the PI and funding agency regarding study progress, termination, or trial modifications. Interventions may be discontinued if recommended by their treating clinician. In addition, Participants are able to discontinue interventions at any time for any reason.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This pilot study is a single-arm clinical trial. The primary objectives **(See Appendix L, Feasibility Outcomes)** are to evaluate the feasibility, safety and acceptability of an integrative care pathway that includes chiropractic care, for the coordinated care for Veterans Administration (VA) patients with chronic low back pain (cLBP), with an emphasis on those with mental health comorbidity, in preparation for the conduct of an appropriately powered multi-site randomized controlled trial (RCT). The secondary objectives are to collect study outcomes at the baseline visit (BV) and at weeks 3, 5, 7, and 10 to: 1) assess the success of collecting outcomes; 2) determine the outcome measures to use in a future RCT; and 3) determine preliminary intervention effect sizes and variability to aid in sample size determination for a future RCT.

All participants will be asked to complete study outcomes **(See Appendix N, Study Assessments)** which include the Roland Morris Disability Questionnaire (RMDQ), Brief Pain Inventory (BPI), as well as the Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder 7-item Scale (GAD-7), Post-traumatic Stress Disorder Checklist-Civilian Version (PLC-C), Alcohol Use Disorders Identification Test (AUDIT), Keele Start Back Screening Tool (STarT Back), self-care behaviors, Healing Encounters and Attitudes Lists (HEAL), Expectations for Complementary and Integrative Treatments Questionnaire (EXPECT), and Pain Intensity, Enjoyment of Life, General Activity Assessment Tool (PEG) questionnaires, and the Pain Assessment Screening Tool and Outcomes Registry (PASTOR) assessment, which includes measures LBP intensity and interference as measured by the Defense and Veterans Pain Rating Scale (DVPRS), pain, disability, mental health, quality of life enjoyment and satisfaction.

9.2 Sample Size

Chronic pain and mental health conditions can be widespread across Veterans of all ages. Because of this, we plan to recruit 40 Veterans 18 and older with cLBP who may or may not have any mental health conditions.

9.3 Definition of Populations

This section is not applicable as this is a pilot, single-arm trial.

9.4 Interim Analyses and Stopping Rules

This section is not applicable as this is a pilot, single-arm trial.

9.5 Outcomes

9.5.1 Primary Outcome

The primary objectives of this clinical trial are to evaluate the feasibility, safety and acceptability of an integrative care pathway that includes chiropractic care, developed through a consensus-based process, for the coordinated care for Veterans Administration (VA) patients with chronic low back pain (cLBP), with an emphasis on those with mental health comorbidity **(see Appendix L)**.

- Feasibility will be assessed by monitoring recruitment, retention, and visit compliance and assessing trial management protocols and ability to meet regulatory deadlines.
- Safety will be assessed by monitoring Adverse Events (AEs).
- Participant and provider perceptions of the pilot will be assessed with a structured, qualitative exit interview.

9.5.2 Secondary Outcomes

To collect study outcomes at BV and at weeks 3, 5, 7, and 10 to determine preliminary effect sizes. Outcome measures include the Roland Morris Disability Questionnaire, BPI, PHQ-9, GAD-7, PLC-C, AUDIT, STarT Back, SF8a, self-care behaviors, HEAL, EXPECT, and PEG questionnaires, the PASTOR assessment, which includes measures of pain, disability, mental health, quality of life and patient satisfaction, and the qualitative exit interview **(see Appendix N)**.

9.6 Data Analyses

Qualitative data analysis will be conducted using NVIVO software (QSR International Pty Ltd., Victoria, Australia). Coding will use inductive and deductive approaches, building on the HEAL instrument as an initial codebook. To enhance trustworthiness of study findings, Dr. Salsbury and another coder will dual code all transcripts using the constant comparative method and thematic content analysis.[87] Coders will meet for frequent reconciliation to establish and refine the codebook and finalize the analysis. Qualitative data will be compared across individuals to understand the range, variability, and areas of consensus and divergence on the benefits and usefulness of the study interventions for managing cLBP and to understand patient perceptions of their VA healthcare environment.

Quantitative data analysis will be done in SAS/STAT (Release 9.4). We will calculate descriptive statistics, including mean, SD, median and interquartile range for numeric variables and counts and percents for categorical variables, for all participants overall, for each cohort, and by sex and race. This will allow us to estimate effect sizes overall and for each cohort. Our primary outcomes are for feasibility as stated in **Appendix L**; there is no need to perform formal data analyses to measure these feasibility outcomes

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data collection for outcome assessments will be completed by participant self-report through REDCap a secure, password protected web-application.

The Lead Data Manager programed the data collection instruments in REDCap and facilitated form testing by users (see more details below).

10.2 Data Management

10.2.1 Data Management of Patient-Reported Outcome Assessments

The Office of Data Management & Biostatistics (ODM) will support data management, provide technical support, and execute procedures for data security and data quality control, storage and back-up. Data security and confidentiality will be carefully monitored. Our data monitoring plan is as follows:

REDCap: Study data will be collected and managed using REDCap electronic data capture tools hosted at Palmer College of Chiropractic. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

REDCap modules will include patient eligibility checks, participant baseline screening questionnaire, participant tracking and report generation. Data entry interfaces will be programmed with appropriate participant flow restrictions, validation schemes and skip patterns. Password protected logins for project personnel will control access to modules and reports within REDCap. REDCap will be developed and tested by data-related personnel on a development server and then published to the training site for further testing and training by other study personnel. After testing is complete the site will be published to the official project site that resides on a secure production web server. The Data Core Manager and REDCap Administrator will monitor the quality of the web applications and related databases, manage change requests and create documentation. All participant questionnaires will be administered via the web which can be completed at any computer available to the participant. During the baseline screening, the participant will confirm an email address that will be used to provide secure access on outcome assessments. Data management and quality control of web forms will be performed using REDCap's real-time, web-based reports.

Web Security: REDCap is secured with Certified Secure Socket Layers (SSL) 256-bit encryption (RSA 2048), hosted (IIS V10.0) and maintained by Palmer College of Chiropractic Information Technology department. It is 21 CFR part 11 compliant. All data collected via REDCap will be stored on an internal MySQL Server 5.7. Palmer servers reside behind a stateful layer 7 hardware firewall with permissions determined by Active Directory. Only select study personnel will

have access to project data, which will be backed up nightly to an off-site server. Fields will be flagged as patient identifiers within REDCap and removed from datasets created for analysis in SAS System for Windows (Release 9.4) by an experienced data manager.

Audio recordings: Digital audio recordings will be encrypted at interview and transferred per electronic data transfer protocol below. Using approved processes we used during the COCOV Aim 1 interviews, digital files will be uploaded to a VA-approved professional service for transcription, with final transcripts reviewed for identifying information, cleaned, and saved to data storage as below.

Data Storage: All data will be stored on a secured internal MySQL Server to which only specified ODM personnel will have access. Reports needed to facilitate efficient project management will be built in the REDCap report modules. Server back-up will be performed nightly by IT. The Windows Server environment is password protected with Microsoft Windows Active Directory and meets HIPAA standards. The Lead Data Manager will generate, transfer and store de-identified datasets on secured servers as requested by the Biostatistician. Copies of final datasets, tables, programs, and documentation will be burned on encrypted DVDs and securely stored on site within a fireproof safe. Standard validation reports will be run after each upload to re-test accuracy of queries and database scripts. The Project Manager will save contact information for recruitment and study participants on laptop. The entire hard-drive will be encrypted using Microsoft BitLocker. All study related data will be kept in secure server environment for 3 years from last budgeted expenditure, at which time only de-identified data will be stored for data sharing purposes.

10.2.2 Data Management of EHR Data:

Members of the Yale Center for Medical Informatics will extract EHR data once a month by programmers experienced in acquiring data from the national databases of the VA Corporate Data Warehouse (CDW). The data will be uploaded into a VA SQL Server database on VA Informatics and Computing Infrastructure (VINCI) workspace for secure storage, query and manipulation of participant data.

Data Cleaning of EHR Data: Quantitative data sources include electronic “data dumps” from the EHR CDW files with multiple records per patient (including pharmacy, inpatient and outpatient visits, administrative codes, and laboratory pathology results). Each of these sources requires inspection, pre-processing, and cleaning prior to data analysis. This process will include: a) Data verification – to assure that data type is correct and within defined range; and b) data merging and creation of datasets appropriate for analysis (frequently de-normalization and variable creation).

Gender, race, and zip code of residence will be gathered from the national patient care database. Age will be calculated on the date of entry into the study. BMI will be calculated from vital signs data height and weight. The presence of medical and psychiatric conditions will be based on ICD-9/10 codes. The classification of alcohol, drug, and psychiatric disorders using VA data will be

based on previously validated methods. Encounters will be defined using clinic stop codes that represent services of interest (e.g. emergency department, pain management, physical therapy). Many domains have been mapped to the Observational Medical Outcomes Partnership (OMOP) common data model to create analyzable variables from the CDW and we will use these as appropriate within VINCI CDW environment.

Data Security and Archiving: Security to protect study data include storing data on the production database servers maintained by VA VINCI environment, and analysis in the VINCI environment with tools such as SAS, R, STATA. In addition, all data will also be backed up to an off-site server on a routine basis. This will protect study data in the event of a disk failure or a catastrophe. In addition, patient IDs will be removed and a study ID assigned to protect patient confidentiality when datasets are created for analysis.

10.2.3 Data Utilization of Iowa City VA Patient Records

Retrospective VA administrative data will be utilized to identify eligible Veterans for study invitation. This data exists on VA servers behind password protected firewalls accessible to researchers who are listed on the IRB and who have completed the annual VA Human Subjects and Privacy Training, as well as VA Research Data Security and Privacy Training. The Electronic records containing HIPAA protected data (computer files, electronic databases, etc.) and the study database will be stored on a server behind the VA firewall. The database folder is only accessible to IRB approved research team members. This project data will be stored on the server, which is maintained, backed-up, and secured in a locked server room by the Iowa City VA's The Office of Information & Technology (OI&T) department. The server can only be accessed by individuals with an OI&T-created network account. Data are further secured using network directory permissions assigned by OI&T at the direction of the Principal Investigator (PI). This ensures that only study personnel with the approval of the PI (in accordance with IRB requirements) have access to identifiable human subject/patient data. Additionally, files on the network that contain identifiable human subject data are password protected, and individuals accessing the server on a client machine are instructed to password protect their screen saver in order to maintain data security. All data entry and analysis will occur on VA owned servers and desktop computers.

10.3 Quality Assurance

10.3.1 Training

Project team members will coordinate with VA department administrators to identify providers willing to participate in the pilot study (1-2 DCs, 1-2 primary care providers, and 1-2 mental health providers) and establish training modules during lunch times and presentations on at least two occasions, once prior to initial of recruitment and within six weeks of initiation of data collection. The format will be similar to that used in the COCOA Clinical Trial.[52;88] We will also use email to communicate study updates to providers. Training will begin with an inter-professional discussion of the background and expertise of team members.

We anticipate that integrative care model training will enable each provider to learn how their roles can facilitate MSK and mental health care for common patients. At subsequent trainings, we will introduce evidence-based chiropractic treatment protocols and the integrative care pathway, including referral processes and communication logistics. Training focused on diagnosing and triaging mental health conditions will be available to providers through online continuing medical education materials provided through the VA.

All key personnel have completed the required education on the protection of human research subjects. For Iowa City personnel, this includes training provided by the University of Iowa Human Subjects Office and the Iowa City VA Medical Center. The University of Iowa and Iowa City VAMC require that all personnel complete human subjects training before they can engage in a research study. The University of Iowa IRB keeps a database with the training records and ensures all Investigators are certified. The IRB offers a web-based training through the CITI Company, or a face-to-face training with IRB members. Both trainings provide a history of ethical guidelines in human subjects protections, how federal regulations have evolved, the composition and duties of an institutional review board (IRB), the requirements for informed consent, the different types of IRB review, and investigator responsibilities.

10.3.2 Steering Committee

The study Steering Committee is responsible for coordinating and overseeing the day-to-day operation of the clinical trial. Weekly meetings, in person and via teleconference, will be held to ensure the study remains on schedule, as well as troubleshoot issues and ensure compliance with the study protocol. Within these meetings, the committee will discuss trial progress, data safety monitoring, recruitment and IRB communication. If required to address urgent concerns, additional meetings will be scheduled. The PM will monitor recruitment; assessment completion; protocol deviations and other clinical trial data and report this information to the steering committee on a weekly basis. Steering Committee members are listed in section 12.

10.3.3 Metrics

Progress on feasibility outcomes and feasibility metrics, **as outlined in Appendices L and M**, will be reported and reviewed on a monthly basis.

10.3.4 Protocol Deviations

Study events will be classified into three categories: Protocol deviations, protocol violations, and unanticipated events. A *protocol deviation* will be defined as any variance in the approved study protocol, criteria or procedure that does not affect the participant's safety, rights, welfare or the integrity of the study and its resultant data. *Protocol violations* are deviations that increase the risk or decrease the benefit and/or affect the participant's rights, safety, welfare and/or integrity of the resultant data. Events that do not meet the above definitions but may affect the rights, safety, welfare and/or integrity of the resultant data will be classified as *unanticipated events*.

All study events will be reviewed by the PI at the PCCR. Details of these events will be recorded to ensure proper reporting in accordance with all regulatory

bodies. IRB submission of study events will be dictated by the reporting requirements for each IRB associated with the study. It is important to note that any event that may have an effect on the safety or rights of the volunteer, or the integrity of the study will be promptly reported to the DSMC.

10.3.5 Monitoring

Data management and quality control monitoring of REDCap will be performed by the Lead Data Manager. Automated reports will be viewed by the Lead Data Manager and Project Manager to determine if quality improvement actions must occur such as improved documentation, protocol revisions or personnel retraining. Final project datasets will be assembled by transferring data from REDCap to SAS System for Windows (Release 9.4). The Lead Data Manager will write and test SAS programs to create datasets as requested by the Biostatistician.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol, the informed consent document **(Appendix H)**, and any subsequent modifications will be reviewed and approved by the IRBs responsible for oversight of the study, which include the Palmer College of Chiropractic IRB and The University of Iowa/Department of Veterans Affairs IRB-03.

11.2 Informed Consent Forms

Each participant will sign informed consent and related HIPAA documents before participating in study-related activities. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Upon signing, each participant will receive a copy of the consent form and this fact will be documented in the participant's record. In addition, copies of ICD and HIPAA forms will be given to ICVAHCS human subjects monitor on an annual basis.

11.3 Participant Confidentiality

To maintain participants' confidentiality, all data collected will be stored at Palmer on a secured encrypted MySQL Server to which only specified ODM personnel will have access. Any reports needed to facilitate efficient project management will be built in the REDCap report modules. Server back-up will be performed nightly by IT. The Windows Server environment is password protected with Microsoft Windows Active Directory and meets HIPAA standards. The Lead Data Manager will generate, transfer and store datasets on secured servers as requested by the Biostatistician. Copies of final datasets, tables, programs, and documentation will be burned on encrypted DVDs and securely stored on site within a fireproof safe.

A unique system generated participant identification number (PID) will be assigned during initial consent. The PID is not linked or derived from any participant related information. Identifiable data will be used for contact purposes only during the recruitment and study participation phases. After the participant has completed the study

all 18 individually-identifiable information will be removed from study related data sources. Only the participant ID will remain as an identifier for data management and analysis purposes.

Any data, forms, reports, audio recordings, and other records that leave the site will be identified only by a PID to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB or the NCCIH. All study staff will be trained in confidentiality procedures and will receive the required Department of Veterans Affairs data security training. Consistent with VA policy, participants' participation will be required to be noted in their medical chart.

A study issued mobile phone will be used by the project manager to communicate with participants. This device will be password protected, with the PM and the Data Core Manager being the only persons with the password. Communication will consist of calls or text messages, however, participant information such as name and phone number will be deleted from the device. No protected health communication will be discussed via text message.

11.4 Study Discontinuation

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

12. COMMITTEES

Steering Committee Members:
Members of the COCOV Steering Committee include Christine Goertz, DC, PhD, Anthony Lisi, DC, Stacie Salsbury, PhD, RN, Robert Vining, DC, Cynthia Long, PhD, Robert Wallace, MD, MS, Thad Abrams, MD, MS, Lance Corber, MSITM, and Janice Hubbard, DC, MS.

Data and Safety Monitoring Committee:
An NIH/NCCIH approved DSMC will consist of individuals independent of the participating sites. Members have expertise in chiropractic, medicine, psychiatry, epidemiology, clinical trials, and biostatistics. The DSMC will meet at least twice per year either in person or by teleconference. The DSMC will approve the study protocol, informed consent, and human research participant protection procedures before trial implementation. To monitor trial data, the DSMC will review status reports prepared by the trial biostatistician that include recruitment accrual; enrolled participant baseline characteristics and other enrollment data; follow-up assessment completion; treatment compliance; study protocol deviations and other clinical trial data. To monitor participant safety, the DSMC will review reportable adverse events every six months and will assess any serious adverse events upon report receipt. Given the nature of the intervention under study, no formal stopping rules will be used. The DSMC will make recommendations to the PI and funding agency regarding study progress, termination, or trial modifications.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee.

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15. SUPPLEMENTS/APPENDICES

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