This proposal is in response to VA Rehabilitation Research & Development (RR&D) “Solicitation of Applications for Chronic Pain Treatment and Management” (IL-12-2005-002). We refer to this study as the Evaluation of Stepped CARE for Chronic Pain (ESCAPE) in Iraq/Afghanistan Veterans trial. Our highly experienced, multidisciplinary team of VA investigators will conduct the ESCAPE trial. We are excited and well positioned to conduct the ESCAPE trial given our experience in the areas of pain, depression, and deployment health.

A. RESEARCH OBJECTIVES

Pain is a critical health problem nationwide: 57% of US adults suffer from chronic or recurrent pain. Pain is the most frequent symptom reported in the community and primary care setting, and accounts for nearly 20% of all ambulatory visits. Chronic pain costs an estimated $100 billion each year in health care services and lost productivity and is the most common cause of work disability. Chronic pain is frequently accompanied by psychiatric disorders that add to patient suffering and complicate treatment.

Pain is a critical health problem among veterans. Pain was the most frequently reported symptom in Persian Gulf War veterans and associated with mental disorders and work loss. The deleterious impact of chronic pain on quality of life and function are well known. Despite the prevalence and negative impact, there have been relatively few intervention studies to address chronic pain and none among Operations Iraqi and Enduring Freedom (OIF/OEF) service members (active duty personnel and veterans). The absence of studies is concerning because chronic pain may prove to be even more prevalent and disabling in these veterans than for previous combat veterans due to the high combat intensity of the current conflicts. Enormous challenges lie ahead for the VA as OIF/OEF veterans return home and seek care in our facilities for pain, given its prevalence and morbidity and the complexity and cost of managing pain.

Numerous studies have documented inadequate pain management in a variety of settings. Although several guidelines have been published, empirical evidence is limited for effective treatments, and some treatments are controversial (e.g. use of opioids for non-malignant pain). Despite the lack of clear treatment guidelines, there is consensus that chronic pain management is complex and requires a multidisciplinary treatment approach. While multidisciplinary pain clinics have been shown to improve pain outcomes, these clinics and services are not widely available. Therefore, research to develop effective approaches to chronic pain management is urgently needed.

To address this need, our long-term research objective is to demonstrate the effectiveness of multi-modal, multi-disciplinary interventions to determine the best combinations of pharmacological and non-pharmacological treatments for chronic pain. Before these goals can be realized, however, it will be essential to develop and test novel, but evidence-based intervention strategies to improve pain care for veterans. It will also be important to conduct large, multi-site studies to demonstrate the generalizability and impact of these intervention strategies on meaningful functional and other pain outcomes. Our work will fill research gaps that will guide management and policy decisions across the VA and DoD to improve care for veterans suffering from chronic, disabling pain.

Through the Evaluation of Stepped CARE for Chronic Pain (ESCAPE) trial we aim to develop and test a stepped-care intervention to improve functional and other pain outcomes in OIF/OEF veterans with chronic musculoskeletal pain. Stepped-care involves starting with lower intensity, less costly treatments initially (Step 1) and “stepping up” to more intensive, costly, or complex treatments in patients with inadequate response (Step 2). We believe a stepped care intervention is innovative and directly addresses the RR&D goal to challenge existing paradigms by incorporating various treatment modalities.

Our study population will be 242 OIF/OEF active duty service members and veterans with chronic and disabling pain of the spine or extremities. Participants will be recruited from the Roudebush VA Medical Center. The study design will be a randomized controlled trial. The stepped care approach will involve 12 weeks of optimizing analgesic use coupled with a pain self-management program (Step 1) followed by 12 weeks of brief cognitive behavioral therapy in participants with inadequate improvement in pain-related disability and pain severity (Step 2). Patients treated in usual care will be the control group. Thus, the primary objective of the ESCAPE trial is to compare the effectiveness of a stepped care intervention vs. usual care in OIF/OEF veterans with chronic and disabling musculoskeletal pain and to

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evaluate the impact of this intervention on pain-related disability, pain severity, psychological distress, and secondary outcomes.

**Hypotheses:**

Our two primary hypotheses are that in OIF/OEF veterans with chronic pain:

1. Stepped care is more effective than usual care in reducing pain-related disability
2. Stepped care is more effective than usual care in reducing pain severity

We will also examine two secondary hypotheses:

3. Stepped care is more effective than usual care in reducing psychological distress
4. Stepped care is more effective than usual care in improving secondary outcomes of
   - Work functioning
   - Health-related quality of life
   - Self-efficacy to manage pain
   - Negative pain beliefs and coping
   - Satisfaction with treatment

**B. BACKGROUND**

**B1. Musculoskeletal pain is the most prevalent, disabling and costly pain condition**

We, as well as numerous other investigators, have established that musculoskeletal pain is consistently the most common, disabling, and costly of all pain conditions (see summary table of our studies in Appendix 1).\[11;12\] The prevalence of musculoskeletal pain ranges between 38% and 47%, among Persian Gulf War and OIF/OEF veterans.\[13;14\] Among individuals reporting musculoskeletal pain, multiple studies have shown that the lower back and legs, especially hip and knee, are the most common sites. The functional and economic impact of musculoskeletal pain on military\[15\] and working populations is enormous.\[16\] Musculoskeletal pain is a leading cause of work absenteeism, underemployment, and unemployment.\[11\] Back and joint pain alone result in an estimated 200 million lost work days per year at a staggering cost of $61 billion in lost productivity.\[17\]

**B2. Chronic pain is frequently accompanied by psychiatric comorbidity and disability**

Literature reviews by us\[6\] and others\[18\] have demonstrated that pain and depression frequently overlap by as much as 30% to 60% and that their combination produces additive effects on adverse health outcomes.\[6\] Musculoskeletal pain comorbid with depression is particularly common.\[19\] Among veterans with chronic pain, the prevalence of depression exceeds 40%.\[20\] Concurrent pain and depression have a much greater impact than either disorder alone on multiple domains of functional status as well as health care utilization.\[6\] While less is known about the interaction between chronic pain and anxiety or post-traumatic stress disorder (PTSD), Otis et al. reported the prevalence of pain to be 45% to 87% in patients with PTSD.\[21\] Furthermore, patients with both pain and PTSD experience more intense pain, more emotional distress, and greater disability than patients with pain alone.\[21\] Comorbidity decreases the likelihood of a good response of either condition to treatment.\[6\] Consequently, integrated approaches to treating comorbid pain and psychological conditions are needed for best outcomes.\[6\]

**B3. Combined treatments are needed to improve outcomes for chronic musculoskeletal pain**

Although several guidelines regarding pain management have been published, the optimal approach is still not well understood. We recently completed a systematic review of chronic pain guidelines which revealed significant variation across different guidelines.\[22\] This variation is explained, in part, by a lack of evidence supporting specific recommendations and the relative dearth of well-designed, intervention studies upon which to base treatment. Pharmacological treatments often provide suboptimal pain relief when used alone,\[23\] and opioids for chronic non-musculoskeletal pain are still somewhat controversial. However, the literature suggests that opioids are indicated for a subgroup of patients\[24\] and long-acting

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opioids offer pain relief, perhaps with less risk of addiction than short-acting opioids. The evidence for a number of non-pharmacological treatments is limited, except for those using cognitive behavioral components for chronic pain. Reviews have demonstrated that multidisciplinary approaches improve patient outcomes, but generalizability is limited because these specialized pain clinics and the high intensity services they provide are not widely available. More research is needed to evaluate the optimal combination of pharmacologic and non-pharmacologic treatments that can easily be applied in non-specialty settings such as primary care.

B4. Stepped care as an approach to sequence interventions for musculoskeletal pain

Stepped care is a framework for sequencing and integrating medical, educational, behavioral and cognitive interventions for pain care, starting with the simplest and least-intensive treatments and increasing intensity (“stepping up”) for patients who do not have a favorable outcome with lower intensity care. Engel et al. also proposed a stepped-care approach for service members who experience deployment-related chronic symptoms and proposed delivery of services tailored to the severity of symptoms. In the case of musculoskeletal pain, simple (i.e. feasible in routine practice), and brief interventions such as analgesic treatment and self-management education may be sufficient to address pain and functional limitations in most patients (step 1). However, some patients may require further treatment due to persistent pain-related disability and high pain severity. These patients may benefit from more intensive interventions such as cognitive behavioral interventions that target resumption of normal activities and address maladaptive thoughts (step 2) that hinder clinical improvement.

B5. Self-management programs are beneficial in treating musculoskeletal pain (step 1)

Self-management has been defined as “the ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition.” For patients with chronic pain, self-management involves a combination of treatment adherence, behavioral change, adapting life roles, managing negative emotions, and coping skills. A systematic review by Newman et al. found strong clinical trial evidence that self-management programs are effective for both low back pain and osteoarthritis (most commonly located in the hip and/or knee), with possible secondary benefits in reducing psychological distress. Furthermore, back pain outcomes may be more dependent on effective self-management than on other treatment approaches.

The success of self-management interventions is theoretically linked to intermediate outcomes such as self-efficacy. Self-efficacy is defined as the confidence to complete a behavior in order to reach a desired goal and is a strong mediator of behavioral change. When an individual feels confident in performing specific behaviors, the efforts toward achieving the end result are marked by more persistence, higher goal setting, greater problem solving, and more expended effort. Conversely, lacking self-efficacy to manage, cope, or function with pain has been shown to be a strong predictor of pain intensity, disability, and depression. Moreover, self-efficacy beliefs have an independent effect on pain avoidance behaviors and disability even after controlling for pain severity and depression.

Kate Lorig’s Arthritis Self-Management Program is the most commonly cited program and has consistently demonstrated effectiveness in improving and maintaining health outcomes and reducing health care utilization among patients with arthritis and various rheumatic conditions, including low back pain. The Arthritis Self-Management Program has been shown to be cost-effective and has led to improved psychological functioning. Specifically, the program focuses on improving perceived ability through action plans, feedback, emotional management, and problem solving strategies. Indeed, self-management programs are the best-established behavioral approach to treatment of chronic pain and may be effectively administered by varying levels of trained individuals in group or individual settings.

B6. Cognitive behavioral therapy is effective for chronic pain (step 2)

Cognitive behavioral therapy (CBT) is a skills-based treatment approach that focuses on teaching patients ways to identify and change maladaptive thoughts, feelings, and behaviors and to replace them with those that are more helpful. While a large randomized controlled trial testing the effectiveness of

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CBT and exercise (alone or in combination) improved the primary outcome of physical functioning, the intervention did not show any benefit for Persian Gulf War veterans with pain (a secondary outcome). However this trial enrolled patients with multi-symptom illness (i.e., subjects had to have at least 2 of the following: pain in 2 or more regions of the body, persistent fatigue, and cognitive symptoms), and the results may not be generalizable to veterans whose principal problem is pain. Strong evidence from numerous other studies supports the benefits of CBT for a variety of pain conditions. Furthermore, systematic reviews by our group as well as others have shown the effectiveness of CBT for somatization, physical symptom syndromes, and chronic pain.

In Morley’s review of randomized controlled trials of CBT for chronic pain, the median number of treatment hours was 16 (range 10-18/h). In recent years, the field of psychology has moved towards six or fewer therapy sessions to address the barriers of resource constraints, lack of insurance coverage, and the fact that most psychotherapy clients attend less than six sessions. Turner et al. demonstrated the benefit of brief CBT in temporomandibular pain. Similarly, brief CBT (i.e. 6 sessions) improved physical functioning in patients with fibromyalgia. Another recent advance has been the advent of telephone based interventions for arthritis and depression care. Telephone based interventions have not been studied in OIF/OEF veterans, but have the advantage of covering multiple, geographically-dispersed veterans and practices.

B7. Conceptual Model for ESCAPE Trial

Table 1 outlines the conceptual model underlying the ESCAPE intervention. A stepped-care model, empirically validated by Von Korff for the management of low back pain in primary care, guides our study. In this framework, step 1 involves lower intensity interventions. Applied to this trial, step 1 consists of optimizing analgesic management coupled with a pain self-management program in OIF/OEF veterans with disabling musculoskeletal pain of the spine or extremities. This level of intervention is brief and relatively simple to deliver. Moreover, analgesics are the most common and pragmatic approach to treating pain, but may be insufficient when used alone. Therefore, step 1 also consists of self-management program that integrates education and behavioral interventions. Step 2, involves brief CBT – an increased intensity intervention reserved for those who continue to have moderate pain-related disability and limited (if any) reduction in pain after 12 weeks of step 1 treatments. CBT identifies problems experienced and negative thoughts. Strategies are then developed to overcome barriers and enhance problem solving skills.

<p>| Table 1. Conceptual model for ESCAPE trial |</p>
<table>
<thead>
<tr>
<th>Care Intensity</th>
<th>Targeted Participants</th>
<th>Intervention</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1 (2 components)</td>
<td>OIF/OEF veterans with disabling musculoskeletal pain</td>
<td>Analgesics and adjuvants coupled w/ self management strategies</td>
<td>Reduce pain intensity, Encourage activity, Provide education</td>
</tr>
<tr>
<td>Step 2</td>
<td>Veterans with persistent pain disability and high pain severity at 12 weeks</td>
<td>Cognitive behavioral therapy</td>
<td>Identify difficulties, Identify negative thoughts, Reframe thoughts, Enhance coping</td>
</tr>
</tbody>
</table>

C. WORK ACCOMPLISHED

The following section describes our extensive experience spanning areas of pain epidemiology, pain and depression comorbidity, and case management, self-management, CBT, and telephone-based interventions. Each of these areas is highly relevant to the design of the ESCAPE trial.

C1. Musculoskeletal pain is the most prevalent and burdensome physical symptom

In a series of 10 studies, we have shown that musculoskeletal pain is one of the most commonly reported physical symptoms in primary care, that back and extremity pain (predominantly hip
and knee) are particularly prevalent, and that each is strongly associated with disability, psychiatric comorbidity, worse health status, and other adverse clinical outcomes.

C2. Pain and depression are often comorbid and have reciprocal adverse effects

In four earlier studies, we have highlighted the high comorbidity of pain and depression and establish that pain and psychological symptoms cannot be evaluated or managed in isolation from one another but instead require an integrated biopsychosocial approach. Other relevant recent studies include:

a) Literature synthesis of pain and depression comorbidity. In a critical review of 169 published articles, we found a high co-occurrence rate of pain and depression, averaging in the 30-60% range. This literature review showed that comorbid pain adversely affects depression, health status, work function, and other clinical outcomes, and that comorbid depression has a similar affect in patients with pain.

b) Prevalence and impact of pain on depression outcomes: results from a clinical trial. In the ARTIST (A Randomized Trial Investigating SSRI Treatment) trial, we demonstrated the equivalency of three SSRI antidepressants in 573 clinically depressed patients. In a secondary data analysis, we found a very high prevalence of pain at baseline, and persistence of pain in over two-thirds of patients despite 9 months of antidepressant treatment. In another secondary data analysis, we found that the greater the severity of pain at baseline, the less depression improved with antidepressant therapy.

c) Pain and depression in the Medical Outcomes Study: 2 secondary analyses. The MOS is a four-year prospective observational study examining outcomes of common medical disorders. We found in a secondary analysis of over 3000 MOS participants that coexisting depression and pain have a profound effect on patient satisfaction, especially when the pain is moderate to severe in intensity. We also found that patients with major depression and severe pain had a three-fold increase in mortality. In another secondary analysis, we compared 1200 patients with self-reported musculoskeletal pain disorders to 2123 patients without such disorders. Increasing pain severity was strongly associated with both increasing depression severity and worse functional impairment.

d) Pain and depression in general medical care: 2 pilot studies. In pilot study 1, we retrospectively examined the distribution of vital sign pain scores – a single-item numeric rating from 0 (no pain) to 10 (worst pain you could imagine) – in veterans presenting for routine medical care at our VA. Of 76,400 clinic visits from 2000-2002, pain was documented in 33% (5% mild, 13% moderate, and 15% severe). In study 2, we surveyed 301 patients in the VA general medicine clinics. Pain was present in 74% of the sample (mild 21%, moderate 31% and severe 22%), and depression was present in 28%.

e) Other consequences of pain disorders. In other related studies of pain, we have shown an overuse of diagnostic imaging, a greater reliance on complementary and alternative medicine, and increased patient dissatisfaction.

C3. Our experience conducting case management effectiveness trials

We have completed two case management studies, collaborated on one, currently enrolling in one, and in the start-up phase of another (see Table 2). The IMPACT trial included case management vs. usual care for late-life depression in which we enrolled 235 primary care patients as part of this multi-site study. Particularly relevant for this project is our experience successfully delivering problem solving therapy by a medical social worker as part of the IMPACT intervention. We recently completed enrollment of 240 patients with poststroke depression in the AIM trial comparing antidepressant care management vs. usual care. And we are midway through enrolling 250 patients for the SCAMP trial, an effectiveness trial comparing a stepped care intervention delivered by a nurse care manager in patients with comorbid musculoskeletal pain and depression. Dr. Kroenke is PI on the INCPAD trial, a telephone-based care management intervention for cancer patients with pain and/or depression. Also, Dr. Kroenke collaborated on the RESPECT study, a randomized dissemination trial of depression care management vs. usual care in 60 community-based practices. In all five trials a nurse care manager was trained in assessing and monitoring symptoms, evaluating treatment adherence, and adjusting treatment. Two of the studies (AIM and SCAMP) have enrolled substantial numbers of veterans at our VAMC.

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Table 2. Case Management Effectiveness Trials for Pain and Depression

<table>
<thead>
<tr>
<th>Trial *</th>
<th>Study Condition</th>
<th>N</th>
<th>Sites</th>
<th>Funding Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT</td>
<td>Late-life depression</td>
<td>1801</td>
<td>8</td>
<td>Hartford Foundation</td>
</tr>
<tr>
<td>RESPECT</td>
<td>Primary care depression</td>
<td>405</td>
<td>60</td>
<td>MacArthur Foundation</td>
</tr>
<tr>
<td>AIM</td>
<td>Post-stroke depression</td>
<td>240</td>
<td>3</td>
<td>NIH (NINDS)</td>
</tr>
<tr>
<td>SCAMP</td>
<td>Musculoskeletal pain and depression</td>
<td>250</td>
<td>5</td>
<td>NIH (NIMH)</td>
</tr>
<tr>
<td>INCPAD</td>
<td>Pain and/or depression in cancer patients</td>
<td>480</td>
<td>12</td>
<td>NIH (NCI)</td>
</tr>
</tbody>
</table>

IMPACT: Improving Mood – Promoting Access to Collaborative Treatment trial
RESPECT: Re-Engineering Systems in the Primary Care Treatment of Depression trial
AIM: Activate patient, Initiate treatment, and Monitor outcomes trial
SCAMP: Stepped Care for Affective disorders and Musculoskeletal Pain trial
INCPAD: Indiana Cancer Pain and Depression trial

C4. Self-management programs improve outcomes in patients with low back pain

Our team has successfully applied Lorig’s Arthritis Self-Management Program,70 to enhance patient self-efficacy and motivation to implement strategies required to manage low back pain. Dr. Damush, a co-investigator on ESCAPE, enrolled 211 primary care patients with acute back pain into a clinical trial, randomizing them to 4½ hours of a pain self-management program or usual care. Among patients in the treatment group, 28.3% attended at least one group class, 62.3% received the intervention by mail, telephone, and audiotapes, and 9.4% received no intervention. Compared to patients receiving usual care, intervention patients reported less disability, reduced fears of movement/re-injury, and improved mental functioning, self-efficacy to manage low back pain, and time spent in physical activity.71

While this trial found both short- and long-term improvements in emotional functioning and self-efficacy to manage symptoms among patients with acute back pain, it also became apparent that alternative methods of program delivery other than group classes are needed to reach a greater portion of patients. Importantly, the majority of patients in this back pain trial by Damush et al34 received the intervention by means other than group classes, consistent with other studies showing that the method for providing a pain self-management program may be tailored to the patient and practice setting.72 Based upon this, our current SCAMP trial uses a flexible approach to delivery: participants chose to receive the intervention individually in person or via the telephone.

C5. Our experience with cognitive behavioral therapy interventions

Collectively, members of our research team have established the effectiveness of CBT in improving work outcomes in veterans with serious mental illness.73-75 Two VA RR&D funded Merit Reviews (Lyskaker, PI) “The Effects of Cognitive Behavior Therapy on Work Outcome in Schizophrenia” and “The Impact of Cognitive Behavior Therapy on Vocational Outcome in Schizophrenia” has informed the current project. The underlying hypothesis for these studies was that self-defeating beliefs common to individuals with schizophrenia were a major source of work difficulties and that CBT has the potential to modify negative beliefs and may lead to improved work performance. To test this hypothesis, Dr. Lyskaker (a co-investigator on this study) developed a manualized CBT intervention of weekly group and
individual sessions to augment work function in 20 individuals with schizophrenia in a work placement program at our VAMC.  

The CBT treatment manual, named the Indianapolis Vocational Intervention Protocol (IVIP), was tested in a randomized controlled feasibility study of CBT compared to support services in 50 veterans. Both arms received work placement. The treatment arm showed significant effects on work function, including a greater number of weeks worked, improved work performance, and negative cognitions (i.e. hopelessness, and poor self-esteem) compared to the control group. Although CBT has been shown to be effective for pain, depression, and serious mental illness, no data exists to examine CBT in OIF/OEF veterans or in the context of a stepped care model.

C6. Significance and relevance to patient care mission

Pain is remarkably common and is the most frequent reason patients seek health care. Each year chronic pain plagues over 50 million individuals and one third will experience severe chronic pain at some point in their lives. Chronic musculoskeletal pain is the most common cause of long-term disability and the related costs in lost productivity are staggering. Preliminary findings suggest that the nature of the current conflicts in Iraq and Afghanistan may place OIF/OEF veterans at an ever greater risk for chronic pain conditions than earlier veterans. These veterans returning home with injuries from explosive devices, motor vehicle accidents, and other battlefield trauma. Adding to the complexity of managing these painful injuries is the high prevalence of psychiatric comorbidity in OIF/OEF veterans.

To increase the visibility of pain, Congress declared the 10-year period of 2001 to 2010 as the “Decade of Pain Control and Research.” Furthermore the VA has pioneered innovative organizational efforts, such as “Pain as the 5th Vital Sign” initiative and the VHA National Pain Management Strategy to effectively address pain among veterans. However, chronic pain is still being under-treated and finding the best combination of treatments to maximize favorable outcomes is needed. We believe multifaceted treatments will best address the oftentimes complicated pain needs of injured OIF/OEF veterans.

The ESCAPE trial directly addresses the VA RR&D goal to develop multidisciplinary, multimodal, and systematic approaches to reduce suffering in veterans experiencing chronic pain. This study will extend our current understanding of sequencing of multifaceted treatments involving analgesics, self-management strategies, and brief cognitive behavioral therapy. Lessons learned from the stepped care intervention can be adapted for use across VA facilities leading to more effective collaboration between organizations. For example, since the intervention relies on telephone delivery and care manager contacts it has the potential to be applied across multiple geographically dispersed rural or urban clinical settings and may guide other telehealth adaptations of a stepped care approach.

D. RESEARCH DESIGN AND METHODS

D1. Overall Design

Figure 1 highlights key features of the study design. The study population consists of 242 OEF/OIF veterans with musculoskeletal pain of the spine and extremities. Participants will be enrolled from the Roudebush Veterans Administration Medical Center (RVAMC) outpatient clinics. Potential participants will be identified through medical record review and telephone screening. Willing patients will undergo an eligibility interview and those who meet entry criteria and provide informed consent will be enrolled. Participants will be randomized to stepped care or usual care (N= 121 each group). The stepped care intervention will consist of optimizing analgesic and adjuvant treatment coupled with a 12 week pain management program (PSMP) for step 1. Specifically, this will include the following components: (1) education; (2) analgesic and adjuvant management; (3) encouragement to return to normal activities/function; (4) assessment of psychological distress (i.e., depression, PTSD, and anxiety); and (5) active facilitation of mental health consultation if clinically indicated to manage severe depression, anxiety, or PTSD. Step 2 will consist of 12 weeks of brief CBT for those who fail to achieve adequate pain response to step 1. Interviewers blinded to the study hypotheses and treatment assignments will

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conduct outcome assessments at baseline, 3, 6, and 9 months. The two primary outcomes will be pain related disability and pain severity. Secondary outcomes will include psychological distress, work functioning, health-related quality of life, negative pain beliefs, self-efficacy to manage pain, and satisfaction with treatment. Figure 1. ESCAPE study design

D2. Recruitment

D2a. Eligibility

OIF/OEF veterans will be eligible if they meet all of the following criteria summarized in Table 3.

<table>
<thead>
<tr>
<th>Table 3. Eligibility Criteria</th>
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<tr>
<td><strong>Inclusion</strong></td>
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<tr>
<td>• Musculoskeletal pain of low back, cervical spine, or extremities (hip, knee, or shoulder)</td>
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<tr>
<td>• Pain for 3 months or longer</td>
</tr>
<tr>
<td>• Moderate functional impairment defined as Roland Disability Score ≥ 7</td>
</tr>
<tr>
<td>• Access to working telephone†</td>
</tr>
<tr>
<td>• Willing to travel at least once to study sites</td>
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</tbody>
</table>

† Access to a telephone is required because both the intervention and outcome assessments will be conducted via phone

* Exclusion criteria are designed to eliminate potential participants for whom the proposed interventions are inappropriate and/or for whom there may be disincentives for improvement. Most data to apply these criteria will come from the Computerized Medical Record System (CPRS) at RVAMC; which we as a study team have considerable experience using to identify potential participants.

D2b. Identifying and Enrolling Potential Participants

Treating physicians will be informed of the study details and will be asked to provide written consent for the research team to contact their own eligible patients for participation in the trial. Only patients from

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consenting physicians will be enrolled. In our previous trials, over 95% of physicians have agreed to participate. At RVAMC potential participants will primarily be identified by querying CPRS to create a master list of OIF/OEF veterans who have at least moderate pain intensity (pain score ≥ 4) according to the pain scale (“0” no pain to “10” worst pain imaginable) routinely measured in our outpatient clinics within the preceding 6 months. This list of potential participants will be updated monthly during the enrollment period and a recruitment letter, signed by a treating physician, will be mailed to veterans by the research assistant to describe the study. Veterans will be then contacted by phone within a few days to assess eligibility and determine their interest in participating. If the veteran is eligible, verbal consent will be obtained from those who desire to participate. An informed consent statement (see Appendix 2) and HIPPA authorization will be mailed to the patient with a pre-addressed, postage paid return envelope (with phone reminders if not returned). Mailings will include a cover letter reiterating instructions for reviewing, signing, and returning all forms. Additional patients, or those with questions about study participation or the informed consent process, may be consented in person prior to the baseline interview. The OEF/OIF Team at the Roudebush VA, which is comprised of psychiatrists, psychologists, social workers, and primary care providers, will also explain the study to the potentially eligible subjects they treat. If a potential subject indicates interest in hearing more about the study, the OEF/OIF Team will ask if a study member can contact that patient to explain the study in further detail. If the patient agrees, the OEF/OIF Team will collect their contact information, then provide it to the study team.

D2c. Feasibility

To plan for recruitment and assess feasibility, we performed a search of the National OIF/OEF file (from VireC) and our local CPRS to determine the number of OEF/OIF veterans who have received care in our VA (as of 11/18/2005) and the proportion with clinically significant pain associated with functional impairment (pain score ≥ 4). There were 1380 unique OIF/OEF veterans who had been seen at least once in our VA through 11/18/2005. Demographics of this cohort include: mean age of 34.8 years (± 10.3 and range 20-62); 83% men; and a racial mix of 76% Caucasian; 12% African-American; 3% Latino; and 9% other or unknown. Of these, 40% (n = 552) had a pain score of ≥ 4 in the past 6 months and are likely to have at least moderate functional impairment. Notably, 34% and 42% of this cohort screened positive for depression and PTSD respectively and the overlap between pain and depression or PTSD ranged from 15% to 33%.

If we estimate that 75% meet our criteria for disabling pain, this would provide 414 unique patients at our site alone. If 60% of these patients agree to participate at our site alone, we would enroll 248 patients needed in the trial. We have successfully enrolled patients for several similarly sized trials from our VA. Our current SCAMP trial has shown that enrollment exceeds 65% in the VA. In a recent pilot study, 159 (77%) of 206 participants surveyed expressed a willingness to participate in a clinical trial to treat their pain if offered such an opportunity. Therefore, we anticipate no difficulty meeting our sample size requirements. Based on demographic data above, the study sample will include approximately 17% women and at least 15% underrepresented minorities.

D3. Data Collection Protocol

D3a. Measures, Schedule, and Mode of Administration

To evaluate the effectiveness of the stepped care intervention, a comprehensive set of relevant outcomes and key variables that will be measured and when they will be assessed are listed in Table 4. The data collection protocol is informed by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) recommendations and our previous studies.

The baseline interview will take approximately one hour; the 3 month interviews about 30 minutes, and the 6 and 9 month interviews about 45 minutes. As in our previous studies, these assessments will be completed by our research assistants (one at each study site) and conducted by telephone, except for the baseline interview which is done in person. The baseline is conducted as a face-to-face interview to more
effectively establish rapport with participants. Additionally, we have found phone interviews over 45 minutes in length to be burdensome to both participants and interviewers.

Table 4. Outcome Assessment Protocol: Measures and Schedule of Administration

<table>
<thead>
<tr>
<th>Domain</th>
<th>No</th>
<th>Measure*</th>
<th>Items</th>
<th>Time (min)</th>
<th>BL</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covariates</td>
<td>1</td>
<td>Demographics; work status; comorbidity; pain treatment</td>
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<td>9</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 mo</td>
<td>6 mo</td>
<td>9 mo</td>
<td></td>
</tr>
<tr>
<td>Primary Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 mo</td>
<td>6 mo</td>
<td>9 mo</td>
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</tr>
<tr>
<td>Pain-related disability</td>
<td>2</td>
<td>Roland Disability Scale</td>
<td>24</td>
<td>6</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>3</td>
<td>Disability days and score</td>
<td>†</td>
<td>†</td>
<td>X</td>
<td>X</td>
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<td>Pain severity</td>
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<td>Graded Chronic Pain Scale</td>
<td>8</td>
<td>2</td>
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<td>X</td>
<td>X</td>
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<td></td>
<td>5</td>
<td>SF-36 Pain Scale</td>
<td>†</td>
<td>†</td>
<td>X</td>
<td></td>
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<td>6</td>
<td>BPI Interference Items</td>
<td>9</td>
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<td>X</td>
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<td>Secondary Outcomes</td>
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<td></td>
<td>3 mo</td>
<td>6 mo</td>
<td>9 mo</td>
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<td>Psychological distress</td>
<td>7</td>
<td>PHQ-9</td>
<td>9</td>
<td>3</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>8</td>
<td>MCS score of SF-36</td>
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<td>†</td>
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<td></td>
<td>X</td>
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<tr>
<td></td>
<td>9</td>
<td>PRIME-MD anxiety</td>
<td>13</td>
<td>5</td>
<td>X</td>
<td>X</td>
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<td>10</td>
<td>PTSD Screener</td>
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<td></td>
<td>11</td>
<td>PTSD Checklist (PCL-17)</td>
<td>17</td>
<td>4</td>
<td>X</td>
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<tr>
<td>Work Function</td>
<td>12</td>
<td>Work and Health Interview</td>
<td>8</td>
<td>2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Generic HRQL</td>
<td>13</td>
<td>SF-36v2</td>
<td>36</td>
<td>4</td>
<td>X</td>
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<td>Pain self-efficacy</td>
<td>14</td>
<td>Arthritis self-efficacy scale</td>
<td>6</td>
<td>2</td>
<td>X</td>
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<td>Pain beliefs</td>
<td>15</td>
<td>Pain Catastrophizing Scale</td>
<td>10</td>
<td>3</td>
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<td>X</td>
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<td></td>
<td>16</td>
<td>Pain Centrality Scale</td>
<td>12</td>
<td>3</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Somatization</td>
<td>17</td>
<td>PHQ-somatic (12 items)</td>
<td>12</td>
<td>4</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Stressors</td>
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<td>PHQ stressor scale</td>
<td>9</td>
<td>2</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Alcohol Use</td>
<td>19</td>
<td>Audit 10</td>
<td>10</td>
<td>1</td>
<td>X</td>
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<td></td>
<td>X</td>
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<td>Cognitive function</td>
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<td>Sickness Impact Profile</td>
<td>7</td>
<td>1</td>
<td>X</td>
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<td></td>
<td>X</td>
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<tr>
<td>Social function and integration</td>
<td>21</td>
<td>Social Provisions Scale</td>
<td>8</td>
<td>1</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>Deployment exposure</td>
<td>22</td>
<td>Deployment Stress Questionnaire</td>
<td>33</td>
<td>3</td>
<td>X</td>
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<tr>
<td>Physical activity</td>
<td>23</td>
<td>s-IPAQ</td>
<td>7</td>
<td>2</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Occupational</td>
<td>24</td>
<td>COPM</td>
<td>18</td>
<td>4</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

† Number of items or time not listed because this measure is part of another scale listed in Table 4.
* Based on our previous studies, all measures have been found valid with telephone administration

If participants cannot be reached by phone we have employed two strategies to capture all outcome assessments: 1) send a mailed questionnaire to the participant with postage paid, self-addressed envelop to our office; and 2) conduct a face-to-face interview in conjunction with a patient’s clinic visit. Veterans occasionally lack transportation to the in person interviews. In this situation, we have arranged taxi cab rides to and from our VA. To verify accurate response coding by our research assistants, we will record a random sample of interview calls (approximately 5%). To protect against data loss, participant responses

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are entered into two formats: paper and computer. The computer assisted telephone interviews and a study database will be designed in Microsoft Access by our data manager.

D3b. Description of Specific Measures

(1) Baseline patient characteristics will be evaluated with an interview adapted from our previous trials and will include sociodemographics, work status, comorbid medical and psychiatric disorders, and prior treatments for pain.

Pain-related disability will be assessed with three complementary measures:

(2) The Roland Disability Scale is a 24-item pain-specific measure of physical disability originally validated in patients with back pain\textsuperscript{81} and subsequently validated in patients with non-malignant pain problems. Scoring is simple and ranges from 0 (no disability) to 23 (severe disability).

(3) A single item will be asked from the Graded Chronic Pain Scale about the number of disability days and disability score (either work or usual activities) during the preceding 3 months.\textsuperscript{82}

Pain Severity will be measured:

(4) The Graded Chronic Pain Scale (GCPS) is a brief 8-item scale that rates global severity of chronic pain in two domains: intensity and disability.\textsuperscript{82} Rich normative data exists for the GCPS.

(5) The SF-36 Bodily Pain scale contains two items which assess pain severity and interference. A large body of normative data available for this scale.\textsuperscript{83}

(6) The BPI Interference scale has 7 items that rates the interference of pain with mood, physical activity, work, social activity, relations with others, sleep, and enjoyment of life.\textsuperscript{84}

Psychological distress will be assessed with the following measures:

(7) The Patient Health Questionnaire (PHQ-9)\textsuperscript{85} is a brief (9-item) measure of depression severity becoming widely used in clinical and research settings.

(8) The Mental Component Summary Score (MCS) derived from the SF-36 and has been established as a sensitive outcome measure in studies of clinical depression.\textsuperscript{83}

(9) Anxiety severity will be assessed with 13 items from the PHQ anxiety scale.\textsuperscript{86}

(10) The Primary Care PTSD Screen (PC-PTSD) has been validated for use in primary care. The sum of the 4 yes/no items yields a score ranging from 0 to 4, with scores ≥ 3 considered positive for active PTSD.

(11) The PCL-17 is derived from DSM III-R criteria for PTSD, and is used for diagnosis and as a severity measure. The PCL has demonstrated sensitivity and specificity > 70%.\textsuperscript{87}

Other secondary outcomes will be assessed with the following measures:

(12) The Work and Health Interview\textsuperscript{17} is an 8-item scale that has been shown to provide a valid estimate of decreased work productivity due to pain in a large national survey of US workers.

(13) The Medical Outcomes Study SF-36 is a well-established generic measure of health status\textsuperscript{88} that assesses physical and mental functioning in 8 domains and gives highly reliable, valid and responsive summary scores.\textsuperscript{89} It provides both a Physical and Mental Component Summary score.

(14) The Arthritis Self-Efficacy Scale will be used to assess self-efficacy.\textsuperscript{90} This 6-item scale proved sensitive to change in our recent trial of low back pain.

(15) Catastrophizing will be assessed with the Pain Catastrophizing Scale a 13-item scale with three dimensions: rumination; magnification, and helplessness.\textsuperscript{91}

(16) The Centrality of Pain Scale is a 10 item measure to measure how central chronic pain is to a patient’s life.

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(17) The Patient Health Questionnaire somatic symptom severity scale (PHQ-12)\textsuperscript{92} will be used to assess the number and severity of other somatic symptoms.

(18) The Patient Health Questionnaire stressor scale is a 9-item scale of common stressors scored 0 to 20 which has been used in large primary care studies.\textsuperscript{93}

(19) The Audit-C has been validated as an effective screening test and diagnostic tool for alcohol misuse in primary care sample.

(20) Six items were taken from the Sickness Impact Profile to measure cognitive function.

(21) Eight items were taken from the Social Provisions Scale to examine the degree to which social relationships provide various degrees of social support.

(22)

(23) The International Physical Activity Questionnaire (s-IPAQ) is a shorter version developed to measure the amount of health-related physical activity in adults.

(24) The Canadian Occupational Performance Measure (COPM) is a measure designed to detect self-perceived change in occupational performance problems over time.

D3c. Participant incentives

Participants will receive a $20 gift certificate for each completed study interview (baseline, 3, 6, and 9 months) for a maximum incentive of $80 during the course of the study.

D4. DETAILS OF STEPPED CARE INTERVENTION

D4a. Randomization

After providing informed consent and completing the baseline assessment participants will be randomized to stepped or usual care. Randomization will be done by the research assistant using sealed envelopes in which group assignment has been determined from a table of random numbers. Randomization will be blocked in groups of 8.

D4b. Pain Clinical Specialist (PCS)

The stepped care treatment will be delivered by a nurse Pain Clinical Specialist (PCS) trained in providing both components of the stepped care intervention – optimizing analgesic management coupled with pain self-management (step 1) and brief CBT (step 2). We have successfully trained nurse Clinical Specialists to provide antidepressant therapy in our AIM and SCAMP trials, and both antidepressant therapy and problem-solving therapy in our IMPACT trial, and analgesic management in our INCAPD trial. We also have trained individuals to provide a pain self-management program in two trials. Studies demonstrate that non-mental health specialists (e.g nurses) can effectively deliver CBT interventions.\textsuperscript{94-96} The PCS will meet weekly with physician-investigators to review cases; a model of case supervision we have successfully used in 4 trials – IMPACT, AIM, SCAMP, and INCAPD. Also, a physician-investigator will be available at all times to discuss any management issues that arise between the weekly case meetings. Of note, the baseline and the three follow-up outcome assessments will be conducted independently by a research assistant at each site blinded to treatment arm.

D4c. Schedule of Contacts for Intervention Participants

The schedule of PCS phone contacts is outlined in Appendix 5. All participants will have six clinical contacts with the PCS in each step (every 2-3 weeks), for a total of 12. In brief, all participants receive an initial call (baseline or week 0) to assess pain and initiate analgesics/co-analgesics and self-management strategies and a follow-up call at 1-2 weeks to assess pain severity, response to treatment, adherence, and adverse effects. A draft script for the telephone contacts based upon our prior trials is included in Appendix 6. Follow-up PCS telephone contacts will be guided by response to analgesics coupled with self-management strategies, but will occur biweekly on average.

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Making the intervention reproducible requires an algorithmic approach. For this reason, a minimum of 8 phone contacts will follow the initial assessment. From previous studies of care management interventions, however, we know that flexibility is critical to helping some patients make behavioral change and clinically improve. We therefore leave some discretion to the PCS as to whether and when to make supplemental patient contacts. The PCS will keep detailed logs of the timing and content of patient contacts so that we can describe their activities and inform the weekly case management meetings.

D4d. Usual Care Arm

Patients randomized to usual care will receive educational handouts on musculoskeletal pain topics from the Arthritis Foundation and will be informed of their pain severity and that they should seek advice about treatment from a physician. Other than this initial provision of educational materials and advice, there will be no attempt by study personnel to influence pain management unless a psychiatric emergency arises (e.g., suicidal ideation is detected on a baseline or follow-up outcome assessment interview). Patients will be encouraged to discuss problems with their treating physician. A sample telephone script for usual care patients is included in Appendix 7. While randomization by patient means treating physicians will have both intervention and control patients in their practices, numerous effectiveness trials of depression care by us as well as others have shown there is little spillover of the intervention to usual care patients. Minor spillover results in mild contamination of the control group, accompanied by only a small reduction in the observed effectiveness of the treatment group. Moreover, any minor contamination that does occur will lead to a conservative estimate of treatment effect size. This randomization at the patient-level is a superior choice to the large loss in statistical power and potential for additional confounding that can result from use of a group randomized trial design.97

D4e. Intervention Arm: Analgesic Optimization and Pain Self-Management Program (Step 1)

D4e.1. Step 1: Analgesic Optimization Component

While analgesics are the first line of therapy in treating pain, monitoring of pain outcomes and appropriate adjustments (e.g., maximizing doses or switching medications) is often suboptimal. Analgesic management using a nurse-driven algorithm is a core component of our current INCPAD telephone-based care management trial. The PCS will assess what pain medications (and other treatments for pain) have been tried by the patient and whether an adequate treatment trial has been completed, including sufficient dosing of analgesic(s). If inadequate dosage, scheduling, or adherence has been a problem, the PCS may recommend a brief trial of the current analgesic with appropriate dosing and scheduling. The PCS will follow a medication protocol that will allow them to prescribe treatment using written and verbal orders from the physician-investigators. Any changes in analgesics will be in accordance with the World Health Organization (WHO) analgesic ladder (see Figure 2 below).98

After being started on a medication, intervention participants will subsequently be contacted by the PCS one week later to assess medication adherence and potential side effects. If bothersome side effects have occurred prompting non-adherence, discontinuation, or reluctance on the part of the patient to continue the medication, they will be switched to a different medication. An algorithm (see Appendix 5) for these telephone contacts and case management has been successfully used in our AIM and SCAMP trials. Clinical response will be assessed biweekly and management will be discussed during weekly case management meetings as well as consultation with the supervising physician-investigators as needed.

While we provide a rational sequence of analgesic selection, based on the WHO analgesic ladder, we are not testing any particular medication in this trial but, instead, optimal medication management that is both effective and tolerated in an individual patient. Since some

**Figure 2.**

**WHO 3 – Step Ladder**

1 MILD

- Aspirin
- *NSAIDs*
- ± Adjuvants

APAP / Codeine

APAP / Hydrocodone

Oxycodone

Tramadol

± Adjuvants

2 MODERATE

Morphine

Hydromorphone

Methadone

Levorphanol

Fentanyl

Oxycodone

± Adjuvants

3 SEVERE

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veterans started on a given analgesic will need to switch to a different agent, this pragmatic, patient-specific approach approximates the optimal strategy for real-world pain management rather than an inflexible testing of a single drug. At the same time, evidence-based algorithms for drug selection provides a structured approach for the PCS, similar to that effectively applied by clinical specialists in our completed and ongoing trials. We expect a subgroup of patients will be prescribed opioids because of poor response to simple analgesics and/or persistently high levels of pain. After electronic or written prescriptions are entered by the physician-investigators, all study medications will be dispensed through the RVAMC pharmacy. Our study team will interact regularly with Win Turner, RPh, RVAMC’s clinical trial pharmacist, who will oversee study medication dispensing. At study end, treating physicians will be informed of their patient’s medication regimen and it will be left to their discretion to continue or change.

D4e.2. Safety Concerns, Adherence, Side Effects, DSMB, and Adverse Events

Analgesic adherence will be assessed with questionnaire items we have used previously and included in the PCS telephone interview in Appendix 8. We will also use VA pharmacy claims to correlate with self-report data and determine how many patients under-report analgesic non-adherence. Patients taking less than 70% of their medication at any time point will be queried about potential barriers and strategies for enhanced adherence will be discussed. Side effects, as well as aberrant drug-taking behavior, in those prescribed opioid analgesics, will be regularly assessed by both PCS phone contacts as outlined in Appendix 5. The PCS structured follow-up interview is included in Appendix 6.

We will form a local Data Safety Monitoring Board (DSMB) to review our pain assessments and treatments, as well as our adverse event reports (see below), on at least a semiannual basis. Such a board has been used successfully by us in our SCAMP and AIM trials. Board members will consist of a pain specialist, a rheumatologist, a primary care doctor, a nurse, and a statistician. No DSMB members will be investigators on this study. DSMB reports will be generated by the study team, sent to DSMB members for comment, and comments will be compiled and re-sent to all DSMB members for discussion.

An adverse event (AE) is any unintended, unfavorable clinical sign or symptom, any new illness or disease, any deterioration in clinical measures or laboratory values regardless of whether they are considered treatment related. Serious AEs (SAEs) are AEs that are life threatening, result in death, permanent or significant disability or incapacity, or inpatient hospitalization. Adverse events fulfilling one or more of these criteria will be reported as SAEs and will be reported to the IRB and the PI within 24 hours of occurrence. AEs will be recorded on case report forms using a format standard to pain trials. Onset, duration, severity (mild = awareness of signs or symptoms but easily tolerated, moderate = disturbing but still acceptable, severe = unacceptable), whether treatment was required and if so what treatment, and resolution (resolved, intermittent or continuing) will be recorded for each AE. An estimation of likelihood of the relationship between the AE and the analgesic medication, self-management strategies, or brief CBT will be standardized.

D4e.3. Step 1: Self-Management Strategies Component

The pain self-management program (PSMP) to be used in this trial is a core component of our current SCAMP trial of back and knee/hip pain in primary care patients. It is derived from our PSMP intervention proven effective in our primary care trial of low back pain as well as arthritis trials by Lorig, and Von Korff. In conjunction with optimizing analgesic management, veterans will also receive six self-management sessions to discuss the specific strategies of which are listed in Table 5. One module of the self-management manual is included in Appendix 9. The self-management strategies will be delivered by telephone over 6 sessions.

<table>
<thead>
<tr>
<th>Table 5. Pain Self-Management Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient education</td>
</tr>
<tr>
<td>• Identifying pain influences</td>
</tr>
<tr>
<td>• Handling pain flare-ups</td>
</tr>
<tr>
<td>• Minimizing bed rest or inactivity</td>
</tr>
</tbody>
</table>

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The self-management sessions are based on elements of the Transtheoretical Model (TTM) and Social-Cognitive theory and focus on increasing self-efficacy to self-manage musculoskeletal pain. Participants discuss behavioral contracts and problem-solve to sustain behavioral change. The PCS will conduct the sessions using a standardized, written protocol. To promote self-efficacy, the program begins with patient education on the natural history of chronic musculoskeletal pain, emphasizing the intermittent nature of the condition. This is designed to enhance patients' optimism for improved function and coping, but provide realistic expectations regarding the fluctuating course of pain. Common diagnostic and treatment strategies will be discussed. Because patients often expect physicians to order diagnostic tests, the educational component also describes the rationale for ordering (or not ordering) diagnostic tests. Patients are encouraged to discuss both traditional and non-traditional therapies about which they have heard or used. The PCS will promote behaviors found to have at least moderate evidence-based support in the medical literature. In particular, veterans will be encouraged to minimize bed rest and return to normal activities as soon as possible. In addition, education materials will show recommended exercises, including walking. Patients are encouraged to adhere to their physicians' treatment recommendations.

To promote behavior change further, the program includes goal setting. Barriers to engaging in these behaviors are discussed. Veterans choose behaviors to modify, make attempts to modify behavior on their own, self-monitor their progress, and are encouraged to solve their individual problems rather than receive prescribed programs. To promote self-efficacy beliefs, veterans receive individualized feedback about their progress. In addition, patients are encouraged to ask questions of their provider and to use positive talk and relaxation, two strategies that have been successful in self-management programs to manage negative affect. Participants record their behaviors and progress on a standardized form which are discussed at the beginning of each session.

For veterans who have an adequate pain response at 12 weeks, analgesics and other self-management strategies will be continued and reinforced. Patients with inadequate pain response (defined below) proceed to step 2 (brief CBT) at 12 weeks. In this case, the analgesic will not be changed (unless a serious worsening in pain occurs) during CBT. For patients whose pain has not adequately responded after step 2 or in whom relapse is detected during any of the follow-up calls during the 3-month period after step 2, the PCS will recommend that the treating physician consider pain clinic referral or other appropriate specialty consultation (presuming analgesic adherence is confirmed), since a more complex treatment plan may be warranted. We expect at least 30% of intervention patients to have coexisting pain and psychological distress, which will likely complicate management. While this trial is not designed to co-manage both pain and psychological distress, the PCS will regularly assess for psychological symptoms and facilitate referrals to a mental health specialist when needed (e.g. severe depression).

D4f. Intervention Arm: Brief Cognitive Behavioral Therapy (Step 2)

The decision rule for implementing brief CBT at step 2 will be based upon the patient failing to meet both of the following improvement criteria:

- Clinically significant reduction in pain related disability, defined as at least a 2.5 point drop in Roland Disability Scale score from baseline
- Significant pain severity response, defined as at least a 30% reduction in Graded Chronic Pain Scale

Participants who meet only one of the two improvement criteria will be asked if they desire further treatment adjustments. Participants who meet both of the response criteria will continue their current treatment. While requiring both criteria to be met may necessitate a larger proportion of participants proceeding to Step 2, the primary aim of the ESCAPE trial is to reduce pain related disability and psychological distress.
improve pain severity – with combination treatment if needed (i.e., analgesics, PSMP and CBT) for refractory pain. For participants proceeding to step 2, most will probably do so immediately following step 1 because of inadequate pain improvement at 12 weeks. Participants who are found to have comorbid major depression, PTSD, or severe anxiety (PHQ anxiety scale score ≥ 15) will prompt an immediate referral from the physicians-investigators to a mental health specialist for management suggestions.

To compliment the behavioral focus of self-management in step 1, we plan to adapt a manualized program of CBT developed by Dr. Lysaker. The CBT program, called Indianapolis Vocational Intervention Program (IVIP), effectively reduced negative beliefs related to work and led to improved work function (i.e. weeks worked) in patients with schizophrenia.35 IVIP was developed with a basic CBT concept in mind that thoughts affect feelings and, in turn, affect behaviors. Furthermore, the program was modeled after previous CBT interventions.104 For ESCAPE we will draw upon two models used in the IVIP outlined in Table 6. The first is Emery’s “4 A’s model” to help veterans modify dysfunctional cognitions related to pain.105 The second is a problem solving model to frame and overcome perceived barriers to inadequate pain improvement.

<table>
<thead>
<tr>
<th>Table 6. CBT Treatment Models for Step 2</th>
</tr>
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<tbody>
<tr>
<td>4 A’s Model</td>
</tr>
<tr>
<td>• Be aware of dysfunctional cognitions</td>
</tr>
<tr>
<td>• Answer dysfunctional cognitions</td>
</tr>
<tr>
<td>(restructure)</td>
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<tr>
<td>• Act on the more accurate and/or helpful beliefs</td>
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<tr>
<td>• Accept imperfection</td>
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</table>

The CBT intervention will consist of 6 individual sessions delivered by the PCS to participants. Since the PCS and veterans have interacted regularly during step 1, a therapeutic alliance is already established and veterans are familiar with study routines. The first session will involve a discussion of thoughts and feelings about their pain, past treatments for pain, identification of barriers to reducing activity limitation and pain severity, and initiation of cognitive interventions (detailed more below). The biweekly telephone sessions will last a maximum of 45-minutes to optimize participants’ attentiveness and performance required by the cognitive demands of CBT. Each session follows a standard schedule organized into 3 parts (check-in, intervention, and wrap-up) and specific tasks. (See Table 7)

<table>
<thead>
<tr>
<th>Table 7. Format of 45-minute CBT Sessions</th>
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<tbody>
<tr>
<td>Part</td>
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Prior to each session participants are asked to rate the strength and perceived impact for up to four pain beliefs that participants and the PCS have identified together. This exercise sets the stage for problem identification and provides a bridge from the last session. The check-in includes welcoming, a brief pain update on progress and concerns, and collaborative agenda setting of at least one priority item to provide structure for the session. The intervention represents the bulk of the session and includes a discussion of old and new barriers identified while applying cognitive behavioral interventions in a problem oriented manner (i.e enhance problem solving skills). For example, this generally includes addressing a participant’s select dysfunctional cognitions about pain and its impact by disputing their accuracy, and developing a more adaptive

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cognition. The wrap-up involves patient reflection on what was and was not helpful, a PCS summary, collaborative goal setting for the next session, and evaluate progress through bi-weekly ratings of select cognitions and practice assignments. The purpose of these assignments is to apply lessons learned and help assess understanding of the material. To track the success of interventions and provide a focal point of discussion during sessions, participants rate the accuracy of the dysfunctional and alternative cognition which are tracked on two forms (see Dysfunctional Beliefs Tracking Form and the CBT session questionnaire in Appendix 10).

In summary the overriding task during the intervention is for the participant and PCS is to challenge dysfunctional cognitions and modify recognized dysfunctional beliefs veterans hold regarding their pain-related disabilities and interpretations of pain experiences. The ultimate goal for veterans is to learn and maintain more adaptive ways of thinking about themselves and their pain condition, as well as more adaptive behaviors, with the goal of reducing pain disability.

D4g. Assuring Fidelity of PCS Intervention

Procedures to assure treatment fidelity for both steps will be undertaken similar to those used for manualized PSMP in our recent back pain trial and for manualized problem-solving therapy in our IMPACT trial. Briefly, steps will include: (a) extensive PCS training in the manualized PSMP by Dr. Damush and brief CBT by Dr. Lysaker during the start-up period; (b) Observation of Drs. Damush and Lysaker administering treatment sessions in 3 participants; (c) Audiotaping of a sample of treatment sessions delivered by the PCS throughout the study with audiotape review and feedback by Drs. Damush and Lysaker (participants will provide separate written consent for this audiotaping and only participants providing such consent will be audiotaped); and (d) weekly case management conferences in which all participants currently receiving PSMP and analgesic management will be discussed with Drs. Damush, Bair, and Ang and Dr. Lysaker in those receiving brief CBT; and (e) Completion of a checklist for each PSMP and CBT session.

D4h. Other treatments

Participants will continue to be followed by their treating physician for all medical care unrelated to the trial. This includes continuation of other medications as prescribed, clinic visits, and other care as usual. Specifically, use of non-pharmacologic treatments for pain will be permitted (and assessed), both to adjust for co-intervention differences between arms in the analyses and to assess as secondary outcomes.

D4i. Patient withdrawals

Veterans will be allowed to withdraw from the trial at any time. If a veteran withdraws, we will determine the reason for withdrawal. Possible reasons will include: 1) death, 2) worsening of comorbid medical conditions making follow-up impossible, 3) medication side effects, and 4) other. If patients withdraw, we will attempt to obtain their permission to complete the remaining outcome assessments. Data will be analyzed on an intent-to-treat basis.

D5. Statistical Analysis Plan

Using a randomized clinical trial design, the aim of the study is two-fold: 1) assess whether stepped care is more effective than usual care in reducing pain-related disability; and 2) assess whether stepped care is more effective than usual care in reducing pain severity among OIF/ OEF veterans with chronic and disabling pain of the spine or extremities. Relative to Hypothesis 1, we will assess change, between the intervention and control groups, in the Roland Disability Scale score and the days of disability derived from the Graded Chronic Pain Scale (GCPS). Specific to hypothesis 2, we will assess the difference in pain severity, based on the GCPS, between the intervention and control groups. For all analyses described in this study, we will use Statistical Analysis Software (SAS, version 9.1,Cary, N.C.).

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D5a. Baseline and Preliminary Analyses

In the preliminary phase of the analysis, we will tabulate baseline characteristics of the two trial arms for the covariate effects: sociodemographic variables, medical and psychiatric comorbidity, site of musculoskeletal pain, current and prior pain treatment, and treatment adherence. Baseline analyses will include performing descriptive analyses (mean, standard deviation and proportions) of all outcome measures and covariates. The bivariate relationship between covariates and primary outcome measures will be investigated. For continuous variables, we will use analysis of variance methods (or non-parametric equivalents if the data is non-normally distributed). For categorical variables, multi-way contingency tables will be used and odds-ratios calculated. Mantel-Haenszel methods will be applied to summarizing tables where possible and summary odds ratio statistics calculated. Preliminary analyses and plots of the relationships between variables will also serve as a check for outliers. All testing of intervention effects will be based on an intent-to-treat analysis, including patients who do not adhere to study protocols. All scales will be assessed to ensure they meet standard psychometric characteristics.

D5b. Sample Size Estimates

Our sample size estimates are based upon testing the effectiveness of stepped care compared to usual care with respect to the primary outcomes of pain-related disability and pain severity. Our primary measures are continuous variables and include the Roland Disability Scale and the GCPS that provides three separate scores for disability, days of disability, and characteristic pain severity.

To detect a stepped care treatment effect size (mean difference between groups over the study period, divided by the pooled standard deviation) of 0.4 SD on either outcome, our trial would need 100 patients per group, presuming alpha = .05 (two-tailed) and beta = .20 (power = 80%) comparing continuously valued mean treatment scores using a two-sample t-test. The assumed effect size of 0.4 SD is conservative based on previous existing studies of chronic pain treatment. In their meta-analysis of chronic pain treatment modalities, Flor, Fydrich and Turk28 reported average effect sizes of .60 for functional outcomes when comparing patients receiving multidisciplinary treatment to patients in control or usual care groups. In a systematic review (Cochrane) of behavioral treatments for chronic low back pain, van Tulder et al106 reported pooled effect sizes of .62 on pain intensity, .35 on generic functional status, and .40 on behavioral outcomes. Morley et al27 conducted a meta-analysis of data from 25 RCTs of cognitive-behavioral treatment for chronic pain. The median effect size was .5. An effect size of 0.4 is also a clinically relevant difference, as Patrick et al.107 have presented evidence that a 2-point difference on the Roland Scale is likely to be the smallest clinically meaningful effect.

By using mixed-effects repeated measures regression analysis (described below), our power is likely to be somewhat higher. Therefore, our estimated power provides a conservative lower-bound of the likely actual power of our sample size. Based on an estimated 17% attrition of participants (which is more than twice that experienced in our previous care management trials), we will enroll 120 subjects per group in order to assure 100 subjects per group for final analyses to attain our desired level of power.

D5c. Model Development

The intervention effect will be tested using mixed effects models. For continuous variables (such as 9-month Roland disability score, transformed for normality if necessary), we will fit mixed-effects regression models, and use mixed-effects logistic regression models for binary (such as the proportion of participants experiencing a reduction in disability score) and ordinal categorical variables. We apply mixed-effects models to include both fixed and random effects; site and clinic site are fixed effects, physicians (nested within site) are included as random effects. The intervention effect has both a fixed and random component which varies among physicians. The primary (two-sided) test is whether the fixed (mean) intervention effect is significantly different from zero. Although the principal endpoint will be 9 months for each measure, our model will account for the repeated measures design: baseline, 3-, 6-, and 9-month follow-up data on the same participant. We will treat time as a categorical variable and examine the fixed effects for time, intervention group, and their
interactions. An unstructured correlation model will be specified to account for the within-participant correlation. In our models, we will include covariate effects for: sociodemographic variables, medical and psychiatric comorbidity, site of musculoskeletal pain and pain treatment.

D5d. Missing Covariate Data, Participant Drop-Out, and Censoring

There will be instances where participant level covariate information is unobservable, or ‘missing.’ Instances of missing data may occur if information is not recorded. To accommodate ‘missing’ data within the modeling framework, we will investigate patterns of missing covariate data and apply multiple imputation or EM algorithm-based methods. Although all participants will have a baseline visit, there may be several individuals for whom only a portion of the longitudinal outcome measurements are observable. We will carefully examine whether there is differential drop-out. However, we will be limited to perform sensitivity analyses, assuming various responses for the drop-outs, to see what effects they may have on the estimated intervention effect.

D5f. Secondary Analyses

There are several secondary analyses assessing the effectiveness of the stepped care intervention relative to usual care in improving:

- Psychological distress;
- Work functioning;
- Health-related quality of life;
- Self-efficacy and coping with pain;
- Negative pain beliefs;
- Satisfaction with treatment

Analytic techniques will be similar to those previously described, with the dependent variable in separate models being secondary outcomes being secondary outcomes listed above. For these secondary outcome measures, the p-values will be adjusted for multiplicity using the Sidak method (adjusted p-value = 1 – (1 – unadjusted p-value) # tests) analogous to the multiple testing problem.

D6. PROJECT MANAGEMENT PLAN

D6a. Timeline

As shown in Table 8, this is a 3 year project. The first 6 months will involve hiring and training personnel. Important steps will include: (1) finalizing treatment manuals; (2) training the Pain Clinical Specialist (PCS) in assessing pain, managing analgesics, and delivering the self-management strategies and brief CBT; (3) training the research assistants at both sites in the procedures for screening, enrolling, and consenting study participants; (4) programming the electronic medical records to identify potential study subjects based on combat status and pain severity; and (5) obtaining permission from individual treating physicians to approach patients of theirs who might be eligible.

During the next 15 months, we will enroll 242 participants (randomizing 121 each group). Enrollment will average 4 new participants per week (16 per month). Each of the 121 participants entered into the intervention arm will be treated and actively followed for 9 months. Both intervention and control participants will have outcome assessment at baseline, 3, 6, and 9 months. Thus, enrollment will be conducted from months 7-22, and the intervention and outcome assessment phase from months 7-31. Data analysis will begin in month 22 and conducted during the final 14 months of the study (separate baseline, 3 month, 6 month, and end-of-study analyses). Main reports and manuscripts will be prepared months 31-36.

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Table 8. Study Timeline

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<th>Months</th>
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D6.b. Overall project coordination and facilities

Overall project coordination will be led by the study team at the Roudebush VAMC (RVAMC) led by Dr. Bair (PI) and Ms. Sargent (Project coordinator). The study team from RVAMC will have biweekly meetings to ensure a systematic and coordinated approach to delivering and monitoring the study intervention, and to ensure accurate, secure collection and transfer of study data. Prior to study initiation, a study manual will be developed to ensure all study personnel are conducting the study and collecting data in a similar fashion.

RVAMC has secured commitments from the appropriate clinical services to conduct the study (see included letters of support). Drs. Bair, Kroenke, Damush, Schmid, and Sutherland have office, meeting and research space within the HSR&D Center for Implementing Evidence-based Practice (CIEBP) at the RVAMC. The CIEBP includes 8500 sq. ft. of recently-renovated space including 22 finished private offices, 2 large staff areas with modular offices, 2 conference rooms, dedicated research space, and computer resources. Dr. Lysaker’s office is on the 8th floor (two floors up) in Psychiatry and Dr. Ang’s office is located within the same medical center complex and has easy access to CIEBP resources.

D6.c. Investigator roles

The proposed project will be conducted by a strong multidisciplinary team with extensive experience in areas relevant to this study. Specific roles of the research team are outlined in more detail in the budget justification. The efforts of each of the investigators will be coordinated by Dr. Bair and Ms. Nyland to develop plans, review progress, discuss analysis results, and set priorities for the research team. Matthew Bair, MD, MS, has expertise in pain interventions in primary care and chronic pain and depression comorbidity. He will serve as PI and provide overall study direction. Dennis Ang, MD, MPH, is a rheumatologist-investigator with expertise in musculoskeletal pain and depression comorbidity. He will serve as Medical Director for the study and co-lead (with Dr. Bair) the weekly case management meetings. Paul Lysaker, PhD., will contribute expertise in manualized CBT interventions targeting work outcomes and will train the Pain Clinical Specialist (PCS) to deliver brief CBT. Kurt Kroenke, MD, is internationally known for his expertise in symptoms and mental health research in primary care and will contribute senior guidance on all phases of the study. Teresa Damush, PhD, will oversee the patient self-management program and will train the PCS to administer it. Arlene Schmid, PhD, is an occupational therapist-investigator will contribute to developing and testing the conceptual framework underlying effective rehabilitation interventions and relevant outcomes. Jason Sutherland, PhD, is an experienced clinical trial biostatistician on the project. Additional analytic support will be provided by Jingwei Wu.

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MS, who specializes in hierarchical and longitudinal analyses. Christy Sargent, BS, will serve as project manager, and Ada Yeung, MHHS, as the data manager.

D6d. Data Management

Each of the study questionnaires will be programmed into a desktop computer using Microsoft Access. The research assistant will interview the patient and enter data simultaneously into the Access program. Within the Access program, algorithms will be created to check for inappropriate or missed data entry. Computer algorithms will also automatically score the questionnaires and store the summary scales within the same database, as well as determine the appropriate date for follow-up interviews. These data will be backed up daily onto a secured server at RVAMC. Participant social security numbers, names, addresses and other personal information will be restricted to authorized personnel (study teams at both sites) to protect confidentiality. For data analysis and other uses of the data, this information will be removed from the database and be replaced with a simulated identification number. This strategy has been used in our previous clinical trials to efficiently screen and enroll patients, accurately complete follow-up assessment, and protect patient privacy. Our team has prior experience in setting up the protocols for data integrity and data back-up to minimize the risk for lost or inaccurate data.

Ms. Yeung will take the data and place it into the master study database using unscrambled SSN. Data will be stripped of the unscrambled SSN and a study number will be assigned. Standard algorithms will be used to ensure accuracy in data merging. Linking files will be encrypted and stored securely with restricted access.

D7. POTENTIAL LIMITATIONS OF PROPOSED STUDY

1. Study design: We chose a randomized controlled trial of a stepped care approach that will test only the added value of CBT in patients who fail to respond to optimizing analgesic use coupled with a pain self-management program in terms of reduction of pain related disability and severity. It will not compare the relative efficacy of the individual intervention components. While we considered a 3-arm study (or factorial design) comparing combined treatment vs. analgesics, this would involve enrolling at least a 50% greater sample size at a substantially higher cost and thus impractical. More importantly, the sequential efficacy of analgesics coupled with self-management (first line treatments for chronic pain) followed by the addition of CBT for those with an inadequate response would not be tested in a 3-armed design.

2. Attention bias: Intervention veterans will have more contact with the nurse PCS than usual care patients. Potential biases will be minimized in two ways: (1) usual care and intervention patients will have equal amounts of the contact with the research assistants for outcome assessments; and (2) usual care will receive educational handouts on pain and exercises.

3. Reproducibility: Making the intervention reproducible is enhanced using a manualized and algorithmic approach. However, from our previous case management studies we know that flexibility is critical to tailor the intervention to individual patients. Therefore, we leave it to the PCS’s discretion whether and when to make supplemental patient contacts which is similar to clinical practice. Detailed logs of the timing and content of participant contacts will allow a richer description of the intervention and improve reproducibility.

D8. STRENGTHS AND SYNOPSIS OF STUDY

In summary, the ESCAPE trial has a number of strengths, including: (1) a multi-modal, multi-disciplinary intervention designed to improve the management of chronic pain; (2) an innovative stepped-care approach that challenges existing treatment paradigms for chronic pain; (3) a high interest study population (i.e. OIF/OEF veterans); (4) a randomized control design; (5) ample statistical power to detect meaningful differences in our primary outcomes (pain related disability and severity); (6) an explicit decision to include a broad, rather than narrow spectrum of veterans with musculoskeletal pain, such that the study findings will be maximally generalizable and pragmatic; and (7) a telephone-based intervention

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delivered by a nurse care manager that has the potential to be applied across multiple geographically dispersed clinical settings.

Should the stepped care intervention prove effective in reducing pain-related disability and pain severity our next steps will evaluate: (1) the impact of the intervention on work productivity and associated cost benefits; and (2) the intervention’s effect on healthcare utilization and costs. Combining healthcare and intervention costs with health status utilities derived from the SF-12 scores will allow us to project incremental cost-effectiveness of these efforts for the VA.
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