Comprehensive vs. Assisted Management of Mood and Pain Symptoms (CAMMPS)

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SPECIFIC AIMS

Comprehensive vs. Assisted Management of Mood and Pain Symptoms (CAMMPS) Trial

A1. Introduction

I am no better in mind than in body. Both alike are sick and I suffer double hurt. [Ovid]

Two millennia ago, the Greek poet Ovid recognized the "double hurt" caused by comorbid physical and psychological symptoms. Pain is the most common presenting somatic symptom in medical outpatients, and depression and anxiety are the two most common mental disorders. All three conditions are often inadequately treated and result in substantial disability, reduced health-related quality of life, and increased health care costs and utilization. Moreover, they are often inextricably linked in a pain-anxiety-depression ("PAD") triad such that disentanglement is scientifically and clinically impractical. Additionally, the PAD threesome has reciprocal negative effects on treatment response of one another, and additive adverse effects on health outcomes. Although problematic in all practice settings, the PAD triad is especially burdensome in veterans.

We propose to conduct a randomized comparative effectiveness trial – ***Comprehensive vs. Assisted Management of Mood and Pain Symptoms (CAMMPS)*** – to compare two pragmatic interventions (an intensive vs. a low-resource approach) for treating three of the most common, chronic, comorbid and disabling symptoms in veterans: pain, anxiety, and depression. Indeed, CAMMPS will focus on patients with PAD comorbidity, i.e., those having pain plus anxiety and/or depression. Whereas most previous studies have focused on the PAD symptoms individually, the high co-occurrence of these symptoms makes a mono-symptomatic approach impractical as well as suboptimally effective. Single-condition care management programs are not only costly but tend to provide fragmented disease-based care rather than integrated management of the complex patient with comorbidity. In particular, pain is viewed by clinicians and patients alike as primarily a "medical" condition whereas depression and anxiety are considered "mental" disorders. As a consequence, the management of pain and depression/anxiety too often gets carved up between the medical and mental health components of the health care system, rather than being integrated and coordinated.

Our trial will compare two levels of enhancement to usual care for the PAD triad: 1) assisted symptom management (ASM), consisting of automated symptom monitoring and prompted pain and mood self-management; 2) comprehensive symptom management, combining ASM with optimized medication management and facilitated mental health care by a centralized nurse-physician team. The rationale for ASM is preliminary evidence of its effectiveness and its lower use of resources. The rationale for CSM is that the addition of care coordination, optimized medication management for the PAD symptoms, and facilitated mental health care should substantially enhance the benefits of ASM.

A2. Specific Aims and Hypotheses

Our study has one primary aim (#1), two secondary aims (#2,3), and one exploratory aim (#4).

Aim 1. To compare 12-month effectiveness of CSM vs. ASM in improving overall pain and mental health. Our hypothesis is that CSM will be superior to ASM in reducing a composite pain-anxiety-depression severity score.

Aim 2. To compare 12-month effectiveness of CSM vs. ASM in improving specific PAD symptoms. Our hypothesis is that CSM will be superior to ASM in reducing pain, anxiety, and depression severity scores individually.

Aim 3. To compare the effects of CSM vs. ASM on secondary outcomes, including health-related quality of life, disability, health care utilization, treatment satisfaction, and patient and provider perceptions of barriers and facilitators to CSM and ASM.

Aim 4. To explore the relative contribution of each intervention component to overall symptom improvement. These 5 components are automated symptom monitoring, prompted self-management, nurse contacts, optimized medication changes, and facilitated mental health care. Our hypothesis is that each of these components will have a dose-response relationship with the degree of improvement in the primary outcome.

B. BACKGROUND

> "The mind may undoubtedly affect the body; but the body also affects the mind. There is a re-action between them; and by lessening it on either side, you diminish the pain on both."

Leigh Hunt, a 19th century English poet and contemporary of Keats, realized that somatic and psychic pain are inextricably linked and exacerbate one another. This poetic insight portended what clinicians and scientists have repeatedly found, namely that disarticulating chronic physical and psychological symptoms is as hazardous as separating Siamese twins, and that an exclusive focus on treating one type of symptom while ignoring the other imperils the amelioration of both.

B1. Pain is the most common physical symptom and a public health priority

Pain is the most common symptom reported in both the general population and in primary care.[1] Pain complaints account for more than 40% of all symptom-related outpatient visits and over 100 million ambulatory encounters in the U.S. each year.[2] In the United States alone, chronic pain conditions cost more than $500 billion annually in direct medical costs and lost productivity.[1] Pain medications are the second most prescribed class of drugs (after cardiac-renal drugs), accounting for 12% of all medication prescribed during ambulatory office visits in the United States.[3] Clinicians are being pressured to respond to pain as the "fifth vital sign". In House Resolution 1863, the National Pain Care Policy Act of 2003, Congress declared this the "Decade of Pain Control and Research." Indeed, persistent pain is a major international health problem, prompting the World Health Organization to endorse a global campaign against pain.[4] Persistent pain may lead to excessive surgery or other expensive or invasive procedures and is also the leading reason for use of complementary and alternative medicine.[5] Pain is also among the most common reasons for temporary and permanent work disability.[6]

Musculoskeletal pain is consistently the most common, disabling, and costly of all pain complaints.[1,7] Indeed, two-thirds of pain-related outpatient visits are due to musculoskeletal pain, accounting for nearly 70 million outpatient visits in the U.S. each year.[2] In a study assessing pain as the 5th vital sign in 9 VA clinics, more than 80% of all pain complaints expressed by Veterans were musculoskeletal in nature.[8] Two Institute of Medicine reports have summarized the enormous functional and economic impact of musculoskeletal pain on both the working and the retired population.[1,7] Back pain and joint pain alone result in an estimated 200 million lost work days per year.

B2. Depression and anxiety are the two most common psychological disorders in primary care, proving very disabling and costly.

Depression and anxiety are the two most common mental health problems seen in the general medical setting,[9,10] each being present in 10%-15% of primary care patients. They produce substantial disability and decrements in health-related quality of life, often exceeding the impairment seen in patients with chronic medical disorders.[11,12] Depression has been the subject of considerable primary care and public health attention the past several decades. Depressive illness is projected to be the second leading cause of disability worldwide in 2020. The substantial public health and economic significance of depression is reflected by its considerable effect on health care utilization and great monetary costs: $83 billion annually, of which more than half represents lost work productivity.[13]

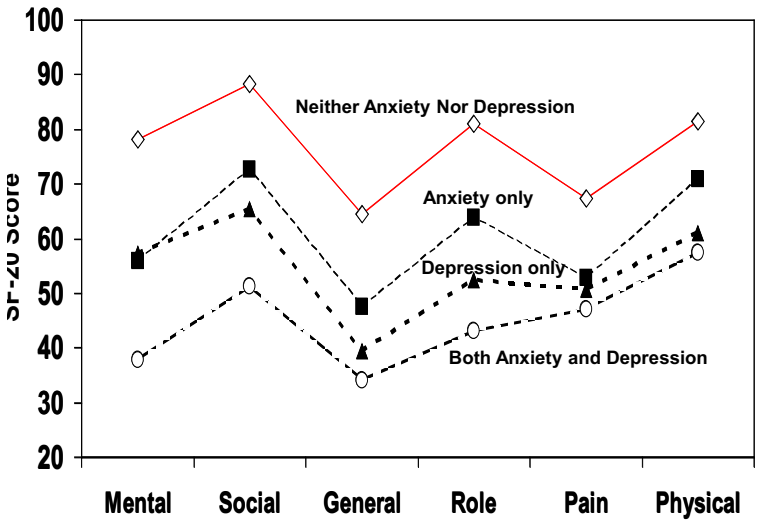
Anxiety disorders are just as prevalent as depression and adversely affects patient functioning, work productivity, and health care costs.[14] Over 30 million Americans have a lifetime history of anxiety, and anxiety disorders cost an estimated $42 billion dollars per year in the United States alone, counting direct and indirect costs.[15] The four most common anxiety disorders (excluding simple phobias which seldom present clinically) are generalized anxiety, panic disorder, social anxiety disorder, and posttraumatic stress disorder (PTSD).[16,17] Moreover, while PTSD is clearly the single most important anxiety disorder in Veterans, recent research shows that other anxiety disorders are also prevalent, undertreated, and disabling in Veterans (see section B3b below). However, despite the significant disability associated with each anxiety disorder and the availability of effective treatments, only a minority (15% to 36%) of patients with anxiety are recognized in primary care[18] and often go untreated.[16] Moreover, anxiety often co-occurs with depression and, when it does, the adverse effects on impairment and resource utilization are additive.[19,20]

B3. Anxiety is a large unmet need in primary care

Depression has been a principal focus of research as well as quality improvement initiatives in primary care for the past 25 years, with chronic pain gaining increased attention the past decade. In contrast, anxiety has been understudied relative to its prevalence and impact summarized in B2 above. Several recent studies highlight the importance of bringing anxiety into the fold.

B3a. Anxiety in Primary Care study. We enrolled more than 2000 adult patients from 15 primary clinics in the United States. A sample of 965 patients underwent a structured psychiatric interview for the 4 most common clinically relevant anxiety disorders in primary care, revealing that posttraumatic stress, generalized anxiety, social anxiety, and panic disorder were present in 8.6%, 7.6%, 6.2%, and 6.2% of the patients, respectively.[16] There was an incremental adverse effect of the number and severity of anxiety disorders on quality of life, disability, and health care use. Additionally, more than 40% of patients with an anxiety disorder reported no current treatment. In an editorial accompanying our paper, Katon and Roy-Byrne wrote: "Anxiety disorders have been the neglected stepchild of primary care–based mental health care. Compared with the extensive research in primary care on the adverse effects of depression on somatic symptom burden, decrements in function, and medical utilization and costs, far less research has been completed on anxiety disorders. Yet, the National Comorbidity Survey has shown that anxiety disorders are the most frequent disorders in the general population and are associated with substantial social and vocational impairment."[21].

There are 2 other findings from this study relevant to CAMMPS.[22] First, of the patients with anxiety and/or depression, 42% had anxiety only, 29% had depression only, and 29% had both anxiety and depression. Thus, if screening programs focused only on depression, 2 out 5 patients with psychological comorbidity would be missed. Second, **Figure 1** on the right shows the effects of anxiety and depression on 6 domains of health-related quality of life (HRQL) as measured by the SF-20 where lower scores indicated worse HRQL. Notably, anxiety had an adverse impact on mental functioning and pain similar to depression, and an adverse effect on other health-related quality of life domains intermediate between depression and no anxiety/depression. Also, for several domains of HRQL (e.g., mental and social functioning), the combination of anxiety and depression was worse than either condition alone.



B3b. Anxiety is a major problem in Veterans. Magruder et al have demonstrated the high prevalence and impairment of untreated PTSD (including subthreshold PTSD) among Veterans receiving care in VA primary care clinics.[23-25] A similar unmet need exists for Veterans in primary care with other anxiety disorders such as panic disorder and social anxiety disorder.[26,27]

B3c. Recent trials demonstrate the treatability of anxiety in primary care. The Coordinated Anxiety Learning and Management (CALM) trial randomized 1004 primary care patients with anxiety disorders to either usual care or a flexibly delivered intervention that provided medication and/or cognitive-behavioral therapy based upon patient preferences and clinical response. The primary care-based intervention was superior to usual care, and was effective regardless of the type of anxiety disorder.[17,28] A smaller trial demonstrated that telephone-based care management improved outcomes in primary care patients with generalized anxiety disorder and panic disorder.[29]

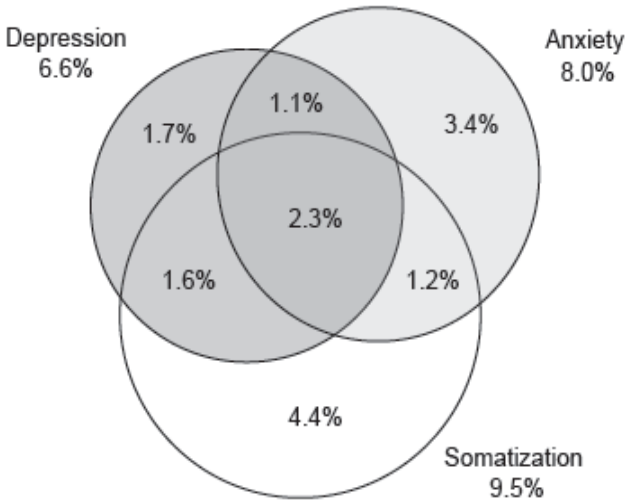
B3d. Adverse effect of comorbid anxiety on depression and pain outcomes. In our SCAMP trial, we found that chronic pain patients with both depression and anxiety had more severe pain, greater disability, and worse quality of life than those with depression only.[30] Longitudinally, baseline anxiety adversely influenced both depression and pain outcomes at 12 months, whereas early improvement in anxiety positively influenced outcomes.[31]

B4. Pain-anxiety-depression (PAD) comorbidity is the norm, making single-condition disease management passé.

A study of 965 primary care patients found high and overlapping levels of pain-anxiety-depression (PAD) symptomatology (**Table 1**).[16] A survey of 2091 primary care patients in 15 U.S. clinics assessed the presence of high depressive, anxiety, and somatic symptom severity with the PHQ-9, GAD-7, and PHQ-15, respectively.[20] Of note, pain symptoms accounted for a substantial proportion of somatic symptoms. As shown in **Figure 2** on the right, a "pure" form of any of the symptom types was less common than comorbidity.[20] Similar results were found in a Swiss study where a survey of 917 general practice patients found that PAD comorbidity was present in 60%, 71%, and 60% of individuals with depression, anxiety, and somatization, respectively.[32] In a study of 340 OIF/OEF Veterans evaluated in a polytrauma clinic, 58.6% had both chronic pain and PTSD , 22.9% had chronic pain only, 9.7% had PTSD only, and 8.8% had neither.[33] PTSD and depression frequently co-occur in Veterans.[34] Finally, our recent analysis of a large population-based study of almost 200,000 individuals randomly sampled from the U.S. verified the high comorbidity and reciprocal adverse affects of depression, anxiety, and pain on each other and on HRQL and disability.[35,36]

Table 1. PAD Severity in 965 Primary Care Patients

Severity *	Pain	Anxiety	Depression
None (0)	12%	35%	35%
Mild (1-3)	36%	30%	31%
Moderate (4-6)	29%	22%	21%
Severe (7-10)	23%	13%	13%
* 0-10 severity scale			



B5. Relative to depression, systems-based interventions for pain and anxiety care have been understudied, with a particular evidence gap for interventions targeting PAD comorbidity

There have been more than 40 randomized controlled trials that have consistently demonstrated that collaborative care or other systems-based enhancements are superior to usual primary care for improving depression outcomes.[37,38] Indeed, the VA has been among the leaders in such research and has developed a robust effort to support the implementation of evidence-based collaborative care for depression throughout its facilities nationwide.[39] A national QUERI initiative (the TIDES model) has systematically disseminated evidence-based approaches.[40] In contrast, there have been only a few published trials supporting collaborative care for chronic pain[41,42] or anxiety[28,29] in primary care. Moreover, only one trial has targeted two PAD symptoms[42], whereas all the rest have focused on a single PAD symptom only.

C. SIGNIFICANCE AND RELEVANCE

C1. CAMMPS is responsive to two HSR&D priority areas

CAMMPS is directly responsive to HSR&D Priority C – Healthcare Informatics, which is described in the Program Announcement: "Healthcare informatics is the integration of biomedical knowledge systems with technology to improve decision-support systems, evidence-based practices, collaboration and continuity of care among providers, and Veteran and provider education." Specifically, sample research

topic #4 under this priority area is to "develop and evaluate decision support systems that incorporate Veteran preferences and enhance management of complex chronic conditions." There are several ways CAMMPS is responsive to this priority area. First, automated symptom monitoring will play a key role in assessing pain, anxiety and depression severity, response to treatment, adherence, and side effects. This facilitates asynchronous data collection in a manner convenient to the patient's schedule and minimizes the "telephone tag" that frequently occurs in standard nurse telecare management. In non-VA cancer populations, this automated approach has been shown to increase the efficiency of care manager time as well as enhance patient satisfaction.[43] Second, prompted pain and mood self-management strategies will be built into the automated system, thereby allowing the technology to advance beyond simple data collection to enhanced treatment as well.[44-46] Third, the system further enhances symptom management by facilitating communication between the Veteran and provider. This is accomplished by enabling the Veteran to request a nurse phone call as well as by flagging certain Veteran reports (e.g., symptom worsening, medication nonadherence or side effects, or a patient desire for treatment changes) and automatically alerting the nurse.

CAMMPS is also responsive to HSR&D Priority Area E – Mental and Behavioral Health, which in the Program Announcement is "broadly defined to include issues ranging from substance use and depression to post-traumatic stress disorders and serious mental illness." Specifically, sample research topic #2 under this priority area is to "evaluate methods to enhance the integration and coordination of mental health services with primary care and specialty services", and sample research topic #3 is to "evaluate innovative strategies to improve earlier identification and treatment of posttraumatic stress disorders and related mental health disorders (substance use and depression)." There are several ways CAMMPS is responsive to this priority area. First, it takes an important next step beyond traditional depression or pain care management programs by adding PTSD and other anxiety disorders. Second, it moves beyond typical care management programs which have supported and enhanced the care provided by primary care physicians to extending this same support to the care provided by psychologists embedded in VA primary care (see section C3 below). Specifically, automated monitoring of depression and anxiety treatment outcomes will facilitate treatment adjustments for patients seen by both primary care physicians and embedded psychologists. Moreover, nurse care manager coordination will enhance both mental health referrals and appointment-keeping.

C2. CAMMPS is highly relevant to the VHA patient care mission.

CAMMPS addresses several issues of great significance and relevance to the VA. First, it provides an integrated approach to three of the most prevalent and burdensome symptom-based disorders afflicting Veterans. While quality improvement initiatives for depression have been disseminated through the TIDES program, coordinated and outcome-based treatment for pain is in its infancy, and systems-based programs for PTSD and other anxiety disorders are likewise lacking. Second, although the placement of psychologists in VA primary care clinics has great potential for improving outcomes, collaborative care that triangulates symptom-based care managers, primary care physicians, and embedded psychologists has not been tested. Also, some of the key components that undergird the effectiveness of collaborative care for depression (e.g., measurement-based care to monitor and adjust treatment; disease registries; coordination of medication management by the physician and psychotherapeutic treatments and follow-up by the mental health professional) are often lacking. Third, the recent increase of mental health professionals in the VA may still be inadequate to meet the huge mental health needs of Veterans. A recent survey of 272 mental health (MH) providers throughout five VISNs found that 40% of MH caregivers cannot schedule an appointment in the desired two-week window (*U.S. Medicine*, Oct 11, 2011). Moreover, 70% of MH caregivers said they did not have adequate staff or space, and 26% said that the need to perform compensation and pension examinations pulled them away from patient care. Thus, enhancing the first-line management of PAD comorbidity in primary care is an important strategy for optimizing the use of high-demand mental health specialty services.

C3. CAMMPS is an important advance that builds upon our completed and ongoing studies.

Table 2 summarizes the key features of our clinical trials to date of pain and depression. ***Four*** innovative and significant features of CAMMPS highlighted in the table include: 1) the addition of anxiety conditions (including PTSD) to the care management program; 2) the comparison to a largely automated

active comparator intervention rather than simple usual care; 3) the collaboration with embedded psychologists in addition to primary care physicians; 4) the collaboration/integration of the intervention with the patient-aligned care teams (PACTs).

The significance of these "next steps" has several additional implications. First, not only is anxiety added (the critical third member of the PAD symptom triad), but CAMMPS focuses on the highly prevalent but much more difficult clinical population that has pain comorbid with depression and/or anxiety. Previous single-condition trials focusing only on pain or psychological conditions (depression, PTSD or other anxiety disorders) are not readily generalizable to the more common clinical scenario where the patient has PAD comorbidity. Second, CAMMPS is the first trial in primary care to simultaneously take on the monitoring and optimization of both analgesic and antidepressant management. Third, the use of outcomes monitoring using validated pain, depression and anxiety measures that are sensitive to change (i.e., measurement-based care) will facilitate treatment adjustments in patients cared for by primary care physicians as well as by psychologists embedded in primary care. Fourth, the comparison with a largely automated intervention will show the incremental benefit of adding nurse care management, optimized medication management, and facilitated mental health care.

Regarding our two ongoing trials, SCOPE focuses only on pain (and not depression or anxiety); is compared to usual care rather than an active comparator; and partners only with primary care physicians and not psychologists. CAMEO likewise focuses only on pain; targets only patients with low back pain receiving chronic opioid therapy; and compares pharmacological management of pain to structured cognitive-behavioral therapy. Neither trial collaborates with PACT. Thus, the 3 trials have distinct aims and interventions.

Table 2. Key Characteristics of Completed and Ongoing Trials

Trial (PI)	N	Prim Care	Pain Site	Prior Pain Rx	% Vets	Intervention Focus			Comparator Group	Partners†			Status
						Pain	Dep	Anx		PCP	MH	PACT	
ESCAPE *(Bair)*	240	Yes	MS	Any	100%	Yes	No	No	Usual care	Yes	No	No	Completed
SCOPE *(Kroenke)*	250	Yes	MS	Any	100%	Yes	No	No	Usual care	Yes	No	No	Ongoing
CAMEO *(Bair)*	450	Yes	Back	Opioids	100%	Yes	No	No	Behavioral intervention	Yes	Yes	No	Ongoing
SCAMP *(Kroenke)*	250	Yes	MS	Any	40%	Yes	Yes	No	Usual care	Yes	No	No	Completed
INCPAD *(Kroenke)*	405	No	Any	Any	8%	Yes	Yes	No	Usual care	Yes	No	No	Completed
CAMMPS *(Kroenke)*	300	Yes	MS	Any	100%	Yes	Yes	Yes	Automated intervention	Yes	Yes	Yes	Proposed

† *Partners* denote clinicians with whom the intervention team collaborates during the trial.
PCP = primary/principal care provider. MH = psychologist embedded in primary care.
PACT = patient-aligned care team

C4. Overall Innovation and Significance of CAMMPS

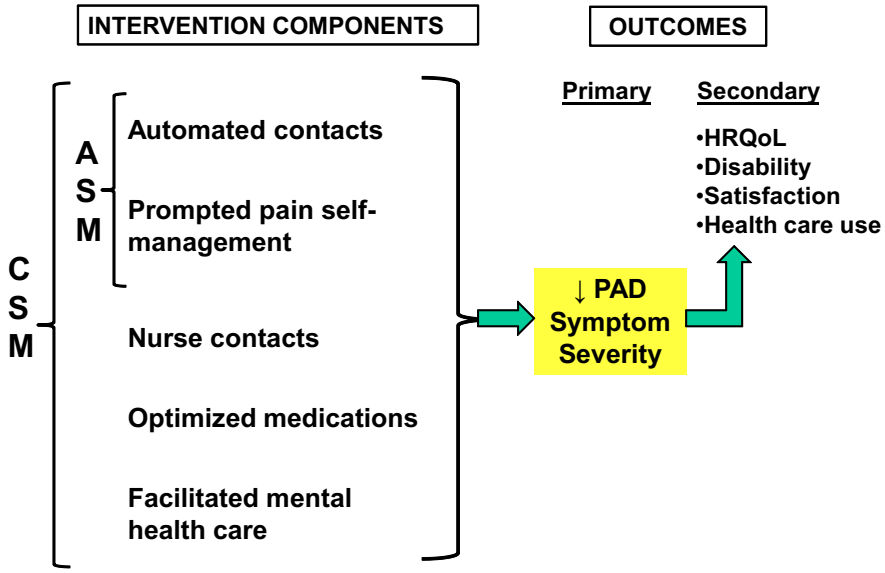
CAMMPS compares a more resource-intensive intervention vs. a low-resource largely automated enhancement of usual care for the major symptom triad among Veterans in primary care. *Innovations* include an integrated approach to PAD symptom comorbidity rather than fragmented care of single symptoms; coordinated symptom management in partnership with both primary care clinicians and psychologists embedded in primary care; the efficient use of health information technology; attention to

physical and psychological symptom comorbidity; and the coupling of self-management with medication treatments. *Significance* is heightened not only by a comparative test of CSM vs. ASM but also by their potential future use in a tailored or stepped care (rather than either-or) approach, their application to symptom management in specialty as well as primary care settings, and their relevance in augmenting symptom management provided by VA telehealth services as well as patient-aligned care teams (PACTs).

D. RESEARCH DESIGN AND METHODS

D1. Conceptual Model

Figure 3 depicts the conceptual model underlying the CAMMPS trial. The assisted symptom management (ASM) arm has 2 components that enhance usual care: automated PAD symptom monitoring and automated prompting of the patient to use pain and mood self-management strategies. The comprehensive symptom management (CSM) arm adds 3 additional components to ASM: nurse contacts; optimized medication regimens for PAD symptoms; and facilitated mental health care. Collectively, these 5 components constitute the active intervention ingredients which lead to an improvement in the primary (proximal) outcome, namely symptom burden as measured by the composite PAD symptom severity (i.e., PROMIS) score. Secondary (distal) outcomes postulated to benefit from reduced PAD symptom burden include health-related quality of life (HRQoL), disability, patient satisfaction, and health care use.



D2a. Overall Design

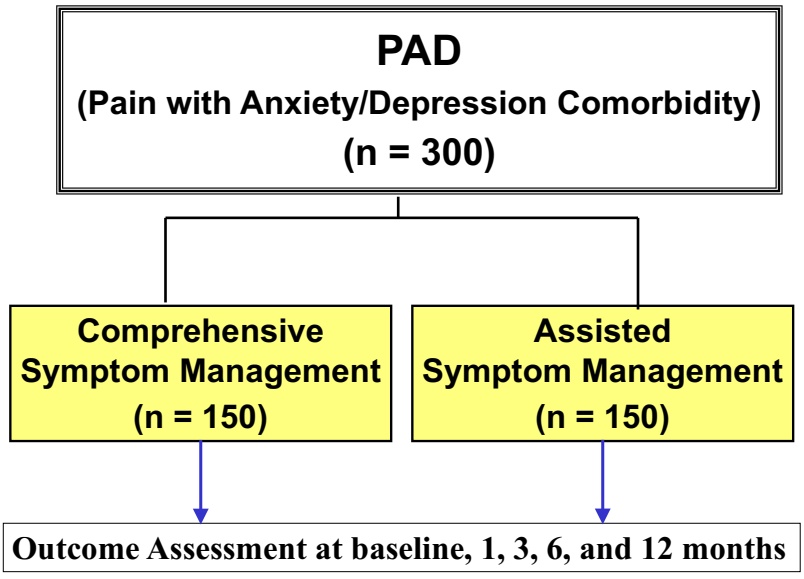


Figure 4 above illustrates the CAMMPS 12-month trial design. Primary care Veterans with pain plus anxiety and/or depression that meet threshold levels of severity and persistence (see section D4a) and who are eligible and provide informed consent will be randomized to one of two treatment arms. One group will receive *assisted symptom management* (ASM) with automated monitoring by interactive voice recording or Internet with prompted pain and mood self-management. The second group will receive *comprehensive symptom management* (CSM) which combines ASM with care coordination by a nurse-physician specialist team that will optimize medication (analgesics/psychotropics) and facilitate mental health care. In short, CAMMPS compares: 1) usual care *plus* assisted symptom management (ASM) vs. 2) usual care *plus* ASM *plus* optimized medication management and facilitated mental health care. Our primary hypothesis is that CSM is superior to ASM in improving both pain and mental health. Outcomes will be assessed at baseline, 1, 3, 6, and 12 months. The primary outcome is a composite pain-anxiety-depression score. Secondary outcomes include individual pain, anxiety, and depression scores; functional status and health-related quality of life; health care utilization; and treatment satisfaction

D2b. Key Questions Regarding CAMMPS Study Design

There are several reasonable questions regarding the CAMMPS study design worth addressing:

1) *Why is assisted symptom management (ASM) selected as an active comparator group?* First, there is preliminary evidence from several trials that automated symptom monitoring with varying degrees of prompted self-management may improve pain and other symptoms in cancer[46] and non-cancer[44,45] populations. Second, ASM uses substantially less resources than CSM so determining its relative effectiveness compared to the more intensive CSM is important from a VA policy and clinical practice standpoint. Indeed, ASM is principally an automated enhancement to usual care that requires a minimal amount of human/clinical resources and could be readily implemented with simple access to either a phone or a computer. In fact, where usual care has already been convincingly shown as inadequate (see #2 below), effectiveness trials increasingly use simple enhancements to usual care as the comparator arm. Third, multiple agencies have called for comparative effectiveness trials: the U.S. Department of Health and Human Services, the Institute of Medicine, the Society for Clinical and Translational Sciences, and the Patient-Centered Outcomes Research Institute have all encouraged a paradigm shift in which head-to-head comparisons are conducted for two or more effective or potentially effective treatment strategies.[47-50] Fourth, ASM will provide immediate symptom-specific self-management strategies to remind patients of the strategies as well as to reinforce potential adherence. Finally, even though CAMMPS is a head-to-head comparison of CSM vs. ASM, the two strategies to enhance usual care could be ultimately used in a stepped care rather than either-or approach.

2) *Why not include a usual care arm?* First, most collaborative care interventions for depression, pain, and anxiety have proven superior to usual care.[28,37,38,41,42,51,52] Second, in these trials, the pre-post effect size within the usual care arm has been modest. Indeed, clinical trials are ethically justified only when there is therapeutic equipoise regarding the treatments being studied.[53] Since patients assigned to the usual care arm in the multiple trials cited above have consistently experienced poor outcomes that are demonstrably inferior to patients assigned to systems-based interventions, the use of a usual care arm would be difficult to defend. Third, if usual care were added as a third arm to the trial, it would not only require a 50% increase in sample size but also mean that two-thirds of patients enrolled would be randomized to either a no-treatment (usual care) or low-resource (ASM) arm. Fourth, ASM is a relatively low-resource enhancement of usual care; our principal question is whether the more resource-intensive CSM strategy of enhancing usual care is superior to the primarily automated ASM approach.

3) *Why require PAD symptom comorbidity?* Studies focusing on single conditions are numerous, with more than 40 trials for depression[37,38], a few for pain[41,42], and one large trial for anxiety.[28] It is increasingly clear that enhanced primary care for a single condition is superior to usual care. However, since PAD comorbidity is more common than a single condition[20], treating one condition to the exclusion of the others or merely adjusting for them as effect modifiers is neither patient-centered, practical, nor optimally effective.

4) *Why include other anxiety disorders besides PTSD?* Several points noted in section B3 bear reiterating. First, 4 anxiety disorders – PTSD, generalized anxiety disorder, panic disorder, and social anxiety disorder – are all prevalent, undertreated, and disabling in primary care patients.[18] Moreover, a third

to half of primary care patients with an anxiety disorder have 2 or more anxiety disorders.[18,19] Second, anxiety disorders other than PTSD are likewise prevalent and undertreated in Veterans.[28,29] Third, the two trials for anxiety disorders in primary care patients showed that integrated treatment was effective regardless of the type of anxiety disorder.[19,30,31] Additionally, our proposed approach using optimized antidepressant therapy and/or psychologist referral based upon patient preferences and clinical response is consistent with VA/DoD guidelines for PTSD (*VA/DoD Clinical Practice Guideline: Management of Post-Traumatic Stress, 2010*, www.healthquality.va.gov) and likewise conforms evidence-based treatment of anxiety disorders other than PTSD.[30]

5) *Why do we expect comprehensive symptom management (CSM) to be superior to ASM?* First, CSM will optimize medication (analgesic and antidepressant) management. Second, the nurse care manager will reinforce self-management strategies, enhance adherence, and overcome patient resistance to mental health referrals. Third, the nurse-physician team will enhance ASM by providing telecare management for more severe, non-responding, or multiple symptoms. Finally, CSM is a collaborative team-based approach that coordinates and triangulates the 3 key partners in PAD symptom management: the specialty team, primary care provider/PACT, and the embedded psychologist.

D3. Enrollment and Randomization

D3a. Eligibility

Individuals will be eligible if they have pain plus comorbid anxiety and/or depression.

Pain must: (a) be musculoskeletal, either localized (in the arms, legs, back, or neck) or widespread (fibromyalgia); (b) have persisted 3 months or longer despite a trial of at least one analgesic medication; (c) at least moderate in severity, defined as a Brief Pain Inventory average severity score of 5 or greater.[54] Persistence for 3 months is a common definition of chronic pain.[55] Musculoskeletal pain accounts for two-thirds of pain-related outpatient visits, leading to nearly 70 million outpatient visits in the U.S. each year.[2] Likewise, musculoskeletal conditions account for more than 80% of pain complaints in Veterans.[8]

Depression must be of at least moderate severity, defined as a PHQ-8 score of 10 or greater with either depressed mood and/or anhedonia being endorsed.[56,57] In previous studies, more than 90% of patients fulfilling this PHQ-8 criterion had major depression and/or dysthymia, and the remaining patients had clinically significant depression with substantial functional impairment.[56,57]

Anxiety must be of at least moderate severity, defined as a GAD-7 score of 10 or greater. In previous studies, the majority of patients fulfilling this GAD-7 criterion had one or more common DSM-IV anxiety disorders (generalized anxiety, panic, social anxiety, and/or posttraumatic stress disorder), and the remaining patients had clinically significant anxiety with substantial functional impairment.[16,57] While the area under the curve is highest for generalized anxiety disorder (.91), it is also good for panic disorder (.85), social anxiety disorder (.83), and PTSD (.83). The positive likelihood ratio for a GAD-7 cutpoint of ≥ 10 for these 4 disorders is 5.1, 2.9, 3.6, and 3.5, respectively.

Composite Mood score must be of at least moderate severity, defined as PHQ-8 + GAD-7 scores of 12 or greater. Because our primary outcome measure is a composite of pain-anxiety-depression scores, individuals with a score of 12 or greater will have sufficient anxiety and depressive symptoms to have mixed-anxiety depression which, combined with elevated pain, should still respond to our intervention.

Excluded will be individuals who: (a) have moderately severe cognitive impairment as defined by a validated 6-item cognitive screener[58]; (b) have schizophrenia, bipolar disorder or other psychosis; (c) are suffering from a severe or complex mental illness or are at high risk of suicide as their condition is unsuitable for a predominantly telecare intervention;(d) are pregnant; (e) have an anticipated life expectancy of less than 12 months. Patients who are on antidepressants but still meet the PHQ-8 and/or GAD-7 entry criterion for clinical depression and/or anxiety are still eligible since our aim is to work collaboratively with their treating clinician to optimize outcomes. Such patients can be considered inadequate responders to their current antidepressant and could have dose titrations or be switched to a different antidepressant, presuming their primary physician (or mental health provider if prescribed by the latter) agrees. This approach has been used in our previous trials. [42,52,59,60]

D3b. Identifying Potential Subjects

Primary care physicians (PCPs) will be informed of the study in detail and provide written consent to approach their patients for participation in the trial. Only patients from consenting PCPs will be enrolled. In our previous trials, over 90% of PCPs have agreed to participate. Electronic medical records will be used to create a master list of individuals who, within the preceding 36 months, have received an ICD diagnosis of a depressive disorder, an anxiety disorder, or a musculoskeletal pain condition. We have identified the relevant ICD codes in our previous studies. This patient list will be updated quarterly during the enrollment period. Individuals on this list will be mailed a letter describing the study and contacted within 2 weeks by telephone to determine potential interest in the study and, if willing, complete an eligibility interview. A similar procedure has been used to enroll Veterans in our SCAMP[42], INCPAD[52], and SCOPE trials.

D3c. Randomization

Eligible patients will be scheduled for an in-person research visit where, after providing informed consent/HIPPA authorization and completing the baseline assessment, study participants will be randomized to one of the two treatment groups. Randomization will be computer-generated using randomly-varying block sizes of 4 or 8 (to assure allocation concealment). Similar randomization has been carried out successfully in our recent trials of pain and depression.[42,52] Randomization will occur at the level of the patient rather than at the physician level for several reasons. First, physicians differ considerably in knowledge, attitudes, and prescribing practices regarding depression, anxiety and pain management, which in turn can serve as important confounders in intervention effectiveness. While multiple physicians will participate, the number will not be large enough to assure that a cluster design (i.e., randomization at the physician level) will result in a balanced distribution of physician-related treatment confounders among study arms. For this reason, patient-level randomization has been the most common design in collaborative care trials.[37,38] Second, numerous trials by us[42,52,61] and others[37,38] have shown that for systems interventions like CSM, contamination of usual care patients is small. A principal ingredient for the effectiveness of collaborative care and other systems-based interventions for depression, pain, and anxiety is the regular monitoring of clinical response and adherence and, as a consequence, adjustments of treatment to optimize outcomes. This degree of regular monitoring and treatment adjustment cannot be readily replicated in usual primary care practice, thus minimizing contamination effects. Third, any spillover to control subjects that does occur will make our estimate of the intervention effect a conservative one.

D3d. Feasibility

A search of the Roudebush VAMC CPRS found there were more than 7000 patients with the musculoskeletal pain conditions who had a primary care visit in the past 12 months. In prior studies, 40%-50% of patients with chronic musculoskeletal pain have had clinically significant depression and/or anxiety. In our VA trials, we have successfully enrolled more than 50% of eligible subjects.

D3e. Inclusion of Women and Minorities

Demographic data on 641 veterans we have enrolled in 3 pain trials at our Roudebush VAMC is summarized in Table 3 below. As shown, the proportion of women and black patients enrolled in our pain trials has increased over the past 7 years. Thus, we expect to enroll 15-20% women and 15-20% Black/African-American patients, while about 5% will be Hispanic.

Table 3. Sex and race distribution in recent primary care pain trials in Roudebush VAMC

Trial	N	Enrollment Period	Women	Race		
				White	Black	Other
SCAMP	200	2005-2007	5.5%	81.0%	16.0%	3.0%
ESCAPE	241	2008-2010	11.6%	76.7%	12.9%	10.4%
SCOPE	200	2010-2012	17.0%	78.5%	17.5%	4.0%

D4. Data Collection Protocol

Table 4 on the next page outlines the study measures and assessment schedule used to address our Specific Aims and detailed under Analysis. The primary outcome measure will be based upon a composite pain-anxiety-depression score (see D4a below). We will also measure clinical, quality of life and health care

use variables. The number of items assessed is similar to our prior trials, and has been well-tolerated with minimal missing data.[42,52,62]

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

Domain	Text #	Measure	# Items		Schedule				
					0 mo	1 mo	3 Mo	6 mo	12 mo
Sociodemographics	1	age, race, sex, education, marital, job status, income	7		X				
Medical comorbidity	2	Checklist of 9 conditions	9		X				
Primary PAD composite *									
• Pain severity/interference	3	Brief Pain Inventory	11		X	X	X	X	X
• Depression severity	4	PHQ-9 depression scale	9		X	X	X	X	X
• Anxiety severity	5	GAD-7 anxiety scale	7		X	X	X	X	X
Secondary PAD composite *	D4a	PROMIS PAD measures	24		X		X	X	X
PTSD severity	6	PTSD Checklist	17		X		X		X
Depression remission tool	7	REMIT depression scale	5						
Clinical response	8	Global Rating of Change	2			X	X	X	X
Somatization	9	PHQ-somatic (12 items)	12		X				X
Functional status and health-related quality of life	10	SF-20 (SF-12 + 8 SF items)	20		X		X		X
	11	Sheehan Disability Scale	3		X		X	X	X
	12	Disability days	2		X		X	X	X
Pain catastrophizing	13	Pain catastrophizing scale	6		X			X	X
Fatigue and insomnia	14	PROMIS fatigue & sleep	8		X		X		X
Anxiety screeners --other	15	MINI-SPIN & OCD item	4		X				
Anxiety severity – other	16	SCL anxiety measure	10		X		X		X
Somatization – other	17	SSS-8	8		X				X
Substance use	18	alcohol, tobacco, illicit drugs	13		X				
Health care & medication use	19	CPRS	n/a						X
Treatment for PAD *	20	PAD-specific treatments	15		X			X	X
Treatment satisfaction	21	PAD-specific satisfaction	4				X		X
Intervention satisfaction	22	Automated monitoring and care management	9						X

***** PAD = pain, anxiety, depression

† SCID has screening questions and skip-outs; thus, number of items asked has wide range.

D4a. Primary outcome measure

The primary outcome measure will be the composite z-score of the main pain, anxiety and depression scales in this trial: the BPI, GAD-7, and PHQ-9, respectively. These 3 symptom scales total 27 items: 11 items for pain, 9 for depression, and 7 for anxiety. . Each of these measures has proven sensitive to change in treatment trials. The composite z-score reflects the 3 symptoms being targeted for treatment in CAMMPS and provides a standardized primary outcome that could not be derived from 3 disparate symptom measures. Calculation of this composite z-score is described in the Analysis section (D9a).

As an important secondary outcome, a composite pain-anxiety-depression score from the PROMIS measures will be calculated. The PROMIS scales include 8 items each for depression and anxiety, and 9 for pain. Conversion tables allow direct conversion of simple summed raw scores from PROMIS symptom scales into T-score values. T-Score distributions are standardized such that a score of 50 represents the average (mean) for the US general population, and the standard deviation around that mean is 10 points. A high score represents greater symptom severity. For example, a person who has a T-score of 60 is one

standard deviation worse than the general population for the symptom being measured. The composite PROMIS score will be the mean of the 3 symptom scores; thus, a patient whose PROMIS pain, anxiety and depression scores are 66, 58, and 53 would have a composite score of 59. Although the PROMIS measures have had extensive validation in cross-sectional studies[63,64], the evidence of their responsiveness (sensitivity to change) in clinical trials or other longitudinal studies is much less than the responsiveness data for the BPI, PHQ-9 and GAD-7. In fact, recent data from our SCOPE trial indicate the PROMIS pain scale may be less responsive than the BPI.

D4b. Other measures

D4b. Other measures

(1) Sociodemographics include age, sex, race, education, marital and job status, and income

(2) Medical comorbidity will be a checklist of 9 common medical disorders that we have shown predicts hospitalization and mortality.[65]

(3) The Brief Pain Inventory (BPI) rates the *intensity* of pain on 4 items (current, worst, least, and average pain in past week), and the *interference* in 7 areas (mood, physical activity, work, social activity, relations with others, sleep, enjoyment of life).[66]

(4) The PHQ-9 has been used in hundreds of research studies as a depression severity and outcome measure and, now translated into more than 80 languages, is among the most widely used depression measures in clinical practice.[56,57]

(5) The GAD-7 is an anxiety severity measure, validated in several thousand primary care patients and increasingly used in clinical research and practice.[57,67] It is also a good first-line measure for estimating the probability of 4 common anxiety disorders in primary care – generalized anxiety disorder, panic disorder, post-traumatic stress disorder, and social anxiety disorder.[16]

Of note, the BPI, PHQ-9 and GAD-7 have all proven sensitive to change as outcome measures in multiple studies.[57,66]

(6) The PTSD Checklist (PCL) is a 17-item validated measure[68] that will be used to assess the presence and severity of posttraumatic stress disorder, a particularly important disorder in military Veterans and one that is commonly comorbid with chronic pain.

(7) The REMIT is a 5-item scale that is useful in predicting depression remission.[69]

(8) The Global Rating of Change assesses overall clinical response of pain and mood, consistent with the IMMPACT recommendations for a 7-item patient global change scale.[70] This scale has been sensitive to change in our previous trials.[42,52]

(9) The PHQ-12 assesses the number and severity of common somatic symptoms and is adapted from the PHQ-15 commonly-used for assessing somatic symptom burden and somatization.[57,71]

(10) The SF-20 will be used to assess generic health-related quality of life, which includes the SF-12 (providing both Physical Component Summary and Mental Component Summary scores)[72]
8 items from the SF-36 to provide the full mental health, social, bodily pain, and vitality scales.

(11) The Sheehan Disability Scale (SDS) is a 3-item scale assessing how much an individual's health condition has interfered with work, family life, and social life over the past month.[73] It has proved responsive to treatment in studies of depression and pain.[52]

(12) Disability days will be assessed with a 2-item measure that asks about the number of days in the past 4 weeks that the individual had to reduce activities by 50% or more for health-related reasons as well as the percent of effectiveness at work.[54,74]

(13) Pain catastrophizing will be assessed with 6-item catastrophizing scale from the Coping Strategies Questionnaire, which has been shown to have strong reliability and validity.[77,78]

(14) The PROMIS fatigue and insomnia 4-item scales will be used to assess these 2 symptoms that are frequently comorbid with pain, depression, and anxiety.[63]

Because the relationship of anxiety with pain has been less well-studied than pain-depression comorbidity, additional scales will be included to increase our understanding of this relationship as well as to determine the operating characteristics and responsiveness of several anxiety scales.

(15) Two anxiety screeners – the 3-item scale for social anxiety disorder and 1 item for obsessive-compulsive disorder.[79]

(16) The SCL-12 anxiety scale is a commonly-used 10-item measure of anxiety severity.[80]

(17) The Somatic Symptom Scale (SSS-8) will be a secondary measure of somatization (Gierk et al, Arch Intern Med, in press). (18) Substance use with be assessed with the AUDIT-C for alcohol[83] as well as questions about the use of tobacco, illicit drugs, and family history.[79]

(19) Health care use and medication use (outpatient visits, emergency department visits, hospitalizations, analgesics, psychotropics) will be assessed by electronic medical record review.[42,52]

(20) Treatments (i.e., medications and nonpharmacological treatments specific to pain and mental health) will be assessed using interview coupled with electronic medical review.[42,52]

(21) Treatment satisfaction overall will be assessed with a 4-item scale used in previous trials.[54]

(22) Satisfaction with the automated and nurse care manager components of the interventions will be assessed with an 9-item survey adapted from our INCPAD trial.[43]

Finally, medications at baseline will be assessed using patient interview coupled with electronic medical record review, as conducted in our previous studies.[42,52]

D4c. Distinction between Primary Research Outcome vs. Clinical Monitoring Symptom Measures

While the composite z-score of the BPI, PHQ-9 and GAD-7 will be our primary outcome measure in CAMMPS, the PEG (a 3-item validated version of the Brief Pain Inventory)[66], PHQ-8, and GAD-7, or a composite score from both the PHQ-8 and GAD-7 will be used to determine trial eligibility as well as to clinically monitor the intervention. It is advantageous for the nurse care manager to use tools to monitor and adjust treatment that are distinct from the outcome measures in order to remain blinded to the PROMIS scores as well as to avoid excessive subject "training" in the primary outcome measure. The PEG, PHQ-8 and GAD-7 are used for study eligibility because these instruments are increasingly used in both practice as well as clinical research and cutpoints for clinically significant pain, anxiety, and depression are well-established.[57,66] For example, the majority of individuals who have a PHQ-8 or GAD-7 score ≥ 10 meet DSM-IV criteria for a depressive or anxiety disorder, respectively, while the remainder have depression or anxiety with at least moderately severe impairment across multiple domains of functional status and quality of life.[57] Likewise, the PEG cutpoints and changes used in CAMMPS have been shown to represent clinically significant pain and pain response, respectively.[66,84]

D4d. Participant burden and rationale for assessment intervals.

Our outcome assessment battery is similar in length to 5 previous trials where participant response and retention has been uniformly high.[42,52,61,62,85] We have used the 4 follow-up assessment intervals in two prior 12-month symptom management trials[42,52] for the following reasons. By month 1, effective treatments should show at least a partial response and, in fact, as much as 75% of the improvement that will ultimately occur does so by month 1.[86] The first 3 months are typically the most active phase of symptom management, making month 3 an important time to assess for symptom remission or additional improvement. The next several months are the highest risk period for symptom relapse, thus justifying a month 6 assessment to determine maintenance of effect, decay or, for self-management strategies, even further benefits. Finally, our primary outcome point is 12 months.

D5. Overview of Interventions

As highlighted in the Conceptual Model (Figure 3) previously and summarized in Table 5 below, there are 5 key components that constitute the interventions in CAMMPS: two are the same in ASM and CSM, while three are unique to CSM. This choice of treatment arms allows for: 1) a low-resource principally automated arm to serve as an active comparator group; 2) testing the added value of the 3 more resource-intense clinician-dependent components – nurse contacts, optimizing medications, and facilitating mental health visits; 3) conducting secondary analyses (see section D9c, Aim 4) to explore the dose-response relationship between each of the 5 components and improvement in the primary outcome.

Table 5. Comparison of Components in the Two Intervention Arms of CAMMPS Trial

#	Intervention component	ASM	CSM
1	Automated contacts (# and total minutes)	✓	✓

2	Prompted pain and mood self-management strategies	✓	✓
3	Nurse contacts (# and total minutes)		✓
4	Optimized medications (analgesic and psychotropic starts and dose changes)		✓
5	Facilitated mental health care		✓

D6. Intervention Arm 1: Assisted Symptom Management (ASM)

There will be 2 principal components to assisted symptom management (ASM): automated symptom monitoring and prompted pain and mood self-management. Automated symptom monitoring was effectively conducted in our INCPAD trial of telecare management of pain and depression[43,52] as well as in our current SCOPE trial of pain management in Veterans. The pain and mood self-management component was developed for our SCOPE trial, having evolved from previous versions in our SCAMP and ESCAPE trials.

D6a. Component 1 – Automated Symptom Monitoring.

Similar to our INCPAD trial[52] and our current SCOPE trial[79], study participants will complete regular symptom surveys either by interactive voice recorded (IVR) telephone calls or Internet (based upon patient preference); both IVR and internet approaches will use push-technology (automated calls or e-mail reminders) to assure equal patient outreach. The schedule will be weekly for the first month, twice a month for months 2-6, and monthly for months 7-12. This "tapering dose" of automated monitoring corresponds: a) *clinically* to the acute phase of initial treatment and dose adjustment or adding/switching medications, followed by less frequent monitoring during the relapse prevention phase; and b) *operationally* to a similar approach used in our recent INCPAD and SCOPE trials. Since all patients will have threshold levels of at least 2 PAD symptoms upon study enrollment, more up-front intensive monitoring with initiation and adjustment of symptom therapy followed by a tapering schedule is both rational and evidence-based.[42,52] The core survey will include 15 items: 10 selected pain and mood items from the PEG, GAD-7 and PHQ-9 to assess severity of the PAD symptoms plus 5 items to prompt use of the pain and mood self-management units.

D6b. Component 2 – Prompted Pain and Mood Self-Management.

A *Pain and Mood Self-Management Program will include approximately 12 hours of web-based instruction divided into 9 units (coping with pain; pain medications; communicating with providers; depression; anxiety; sleep; anger management; moving forward; and problem-solving).* These topics are partly derived from the nurse-administered self-management program in our SCAMP and ESCAPE trials and build upon several VA and non-VA website interactive self-management programs.. Subjects will be instructed in how to use the program by the nurse (CSM group) or project coordinator (ASM group). The web-based delivery of the program along with automated reminders to proceed through the 9 units increases the likelihood of delivery to the patient. Also, the number of units a patient completes will serve as a measure of "dose", which in turn can be examined as an explanatory variable of intervention efficacy.

D7. Intervention Arm 2: Comprehensive Symptom Management (CSM)

D7a. Structured Protocol Overview.

This arm couples nurse care management with ASM, thus testing "combined" therapy vs. "monotherapy" (ASM only). As illustrated in our conceptual model (Figure 3), the nurse provides several active components beyond ASM, including optimized medication management (analgesics and psychotropics) in conjunction with the supervising physician, facilitated mental health care, and enhanced coordination of care with the other key clinical partners – primary care physicians/PACTs and embedded psychologists. CSM is intentionally tailored to each patient's specific PAD symptoms, treatment preferences, and response to therapy; thus, frequency of nurse contacts as well as the specific content of nurse calls will necessarily vary with our "treat to target" approach. However, similar to our INCPAD trial[43,52,74], we will systematically document in detail the frequency, duration, and content of all nursing calls. The time spent on the call reinforcing self-management and discussing medication management will be

individually documented in order to explicitly capture the attention devoted to each component. This will allow us to secondarily examine the independent effect of the intensity ("dose") and content of nurse contacts as a mediator of intervention outcomes.

In our previous and current pain effectiveness trials, virtually all patients desire some optimization of their pain treatment either through starting, adjusting, or switching analgesics or learning pain self-management strategies. Regarding depression or anxiety, however, patients prefer different approaches. For those desiring active treatment, some patients prefer pharmacotherapy (typically antidepressants) while others opt for psychotherapy (talking with a psychologist, psychiatrist or other mental health professional). Since both types of treatment are effective, eliciting and honoring the patient's choice is clinically appropriate. Still other patients are not interested in specific treatment for depression or anxiety initially, but may agree to treatment later once they are followed by the study team and regularly monitored for their symptoms. Thus, patients enrolled in the study will be encouraged to receive active treatment for their depression or anxiety, both initially and during follow-up contacts. However, as this is a real-world clinical trial, accepting active treatment will be optional for each study subject and not a requirement for enrollment. Notably, any patient with severe depression who is actively suicidal (a rare occurrence in our trials) with be managed by our suicidality protocol (section D7h).

The nurse will have *scheduled* telephone contacts with the patient at baseline, 1, 4, and 12 weeks, as well as *symptom-triggered* contacts based upon automated monitoring trend reports (see D7b below). The nurse will monitor trend reports weekly, respond to automated monitoring clinical alerts and patient calls daily, and serve as the coordinating linchpin between patient, supervising physician symptom specialist, primary care physician/PACT, and psychologist. A timely and innovative feature of this trial is the collaboration with not only the PCP but the entire primary care team, specifically the PACT (*Patient-Aligned Care Team*) and the embedded psychologist. Most prior collaborative care trials have focused on the nurse care manager triangulating treatment adjustments with the patient, PCP, and supervising physician specialist.[37,38,87] PACTs in our VA facility have instituted daily "huddles" in which each PCP, his/her team nurse and other relevant PACT team members review key patient issues for the day. Our nurse care manager will work with the most appropriate PACT team member for implementing and coordinating particular treatment recommendations. Also, the nurse care manager will coordinate care of depression and anxiety with the embedded psychologist, providing feedback on depression and anxiety scores to adjust therapy to optimize outcomes. In essence, our CSM model is designed to optimize PAD symptom outcomes by integrating and coordinating management across all primary care team members involved in the veteran's care. This integration of our intervention into our clinics and PACTs is strongly supported by our primary care leadership.

The nurse will have weekly case management sessions with the supervising physician symptom specialist to review all new patients randomized to the CSM group to decide on a treatment plan, as well as enrolled patients not responding to therapy. Of note, the PAD symptoms are seldom urgent or life-threatening but instead require treatment initiation, active monitoring, and treatment adjustments, all of which will typically occur in the CSM arm in a much more expedited fashion than in usual primary care. However, for any symptoms which are more urgent, the nurse care manager will have cell-phone/pager access to the supervising study physician at all times to address the symptoms in a timely fashion. This model of weekly staffing plus on-call physician availability has performed safely and effectively in our prior care management trials.[42,52,59-61]

D7b. Assisted Symptom Management.

All patients randomized to the CSM group will receive ASM as described in Section D6 above. However, ASM will be enhanced in two ways for patients in the CSM group in order to take advantage of the "technology-human" partnership provided by the centralized nurse care manager-physician specialist symptom management team. First, the 15-item ASMsurvey described above in D6a will be augmented by 5 additional items used in our INCPAD and SCOPE trials: global change (i.e., degree of improvement or worsening), medication adherence, side effects, desire for treatment changes, and request for a nurse care manager call.[43,52,74] Second, ASM responses will be tabulated in a trend report on a secure website accessible to the care management team. Trend reports will be reviewed weekly by the nurse care manager. Also, e-mail alerts will be sent to the nurse to trigger patient calls for side effects, a patient request for a treatment change or a nurse call, or missed ASM reports.

D7c. Analgesic Management for Pain.

The nurse care manager will obtain a detailed history of current and past pain medication use. The nurse care manager will then follow the pain medication algorithm developed for this study (**Figure 5**). The pain medication algorithm is derived from our recent systematic review of the literature on pharmacotherapy for chronic pain.[88] When available, VA guideline recommendations were prioritized over those developed for use in non-VA populations. Notably, this algorithm has worked well thus far in our SCOPE trial for the 90 patients (72% of target sample) randomized to the optimized analgesic management arm.

This pain medication algorithm is a step-wise series of brief individual medication trials, and includes tailored steps for different types of chronic pain conditions. Multiple drug classes are included in the algorithm. Data from prior trials suggest that the majority of patients will already be using analgesics at baseline, including opioids in 30-40% of cases. However, the eligibility criteria for the trial require that, despite this, their pain control will be suboptimal. Thus, baseline pain medications may be discontinued, adjusted to achieve an adequate therapeutic trial, or continued with the addition of adjunctive drugs, depending on the patient's history of medication use (e.g., dosing, scheduling, and adherence), therapeutic response, adverse effects, and preferences.

D7c1 Rationale for the Analgesic Algorithm

The rationale and justification for the particular drugs, dosing, and sequencing used in CAMMPS is based upon several factors. First, every recommended medication in the algorithm has demonstrated efficacy for the indications listed from at least 2 randomized clinical trials (RCTs) or, in many cases, from meta-analyses or systematic reviews of multiple RCTs. This evidence has been summarized in our recently-published systematic review.[88] Second, though many medications not listed in the algorithm have been used for treatment of pain, any treatment that does not meet our stringent evidence-based criterion is excluded from the algorithm. Third, for some conditions (e.g., neuropathic pain), treatment guidelines have been issued by more than one organization. In these cases, we determined areas of consensus among the several guidelines so that our algorithm reflects either the unanimous or "majority view" among evidence-based guidelines. Fourth, since all medications in the guidelines have established efficacy in placebo-controlled trials, fewer head-to-head comparisons of analgesics are available. Thus, sequencing is based upon other issues, such as cost, safety, and VA formulary availability. For example, two classes of antidepressants (TCAs and SNRIs) have strong evidence of efficacy for several types of pain disorders. However, TCAs are less expensive and therefore listed first in the algorithm (unless contraindicated in certain groups such as the elderly or those with cardiovascular disease). Fifth, though evidence about the sequencing of analgesics in the algorithm is limited, this is not unlike guidelines we have for many chronic medical disorders. For example, the sequencing of different classes of hypoglycemic drugs in diabetes[89], antihypertensive agents in hypertension[90], and antidepressants in mood disorders[91] is informed by issues of cost, convenience, side effect profiles, and comorbid conditions rather than superior efficacy of one treatment. Sixth, regular monitoring and adjustment of therapy is as important in achieving optimal outcomes as the specific treatment chosen, presuming a menu of equally effective treatments is available.[91]

Figure 5. Analgesic Algorithm*

Step 1:

Simple analgesics

1. Acetaminophen 1000 mg q 6h (max 2000 mg if cirrhosis or ≥ 3 alcoholic drinks/day)
2. NSAIDs: try at least 2;
   a. 1st line: naproxen 500 mg q 12h or 500 q am plus 250 bid (max 1000)
   b. 2nd line: (i) salsalate 1000 mg q 8h or 1500 q 12h (max 3000); (ii) etodolac 300-400 mg q 8h or 500 q 12 h (max 1200); (iii) ibuprofen 600 mg q 6h (max 2400); (iv) meloxicam 7½-15 mg qd; (v) diclofenac 50 mg q 8h (max 150)
3. Consider topical analgesic if neuropathic pain or localized pain (e.g. knee osteoarthritis). For example, capsaicin cream applied 4 times a day for at least 3-4 weeks

Step 2:

Does patient have: (1) neuropathic pain, (2) fibromyalgia/chronic widespread pain, or (3) back pain?

TCAs: try at least two

1. Amitriptyline, start at 10-25, titrate to 100 mg (max 50 mg if taking an SSRI/SNRI)
2. Nortriptyline, start at 10-25, titrate to 100 mg (max 50 mg if taking an SSRI/SNRI)

Step 3

Tramadol

1. Start 25 mg BID or TID and titrate to 100 mg QID (max 300 mg if age > 75; max 100 mg BID if CrCl < 30, 50 mg BID if CrCl <10; max 50 mg BID if cirrhosis)
2. Use concurrent acetaminophen, 500-1000 mg dosed with tramadol TID-QID

Step 4

- **Neuropathic pain**

1. Gabapentin, titrate up to 900-1200 mg tid
2. Duloxetine (60 mg qd) and/or Pregabalin (300-450 mg qd, divided into bid doses)
3. Consider topical analgesic if neuropathic pain or localized pain (e.g. knee osteoarthritis). For example, capsaicin cream applied 4 times a day for at least 3-4 weeks

- **Fibromyalgia/chronic widespread pain**

1. Cyclobenzaprine, titrate to 10 mg TID
2. Pregabalin (300-450 mg qd, divided into BID doses)
3. Duloxetine 60 mg qd or Milnacipran 100 mg qd.

* Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. Gen Hosp Psychiatry 2009;31:206-219.

D7c2 Opioid Management Strategy

Although patients on chronic opioid therapy will be eligible to enroll, the study team will not start opioids or change opioid dosages during the trial without the primary care physician's approval. Instead, our opioid monitoring procedures will enhance the safety of patients already being prescribed opioids who will be monitored in accordance with the recently-updated 2010 VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain (www.va.gov/pain_management).[92] Indeed, our recent medical record review of Veterans receiving long-term opioids in primary care found infrequent use of guideline recommended opioid management practices; for example, opioid agreements, urine drug tests, assessment of alcohol or drug use, and assessment of medication adherence were all present in fewer than one in five records.[93] Thus, our protocol will enhance the safety of opioids already being prescribed. The justification for this approach rather than a strategy which denies opioids to any patient is threefold:

1) It is consistent with both VA and non-VA best-practice guidelines for treatment of chronic pain. Specifically, judicious use of opioids is recommended by the 2010 VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain[92] as well as the 2009 VHA Pain Management Directive.[94] Additionally, guidelines from multiple organizations approve the use of opioids for selected patients who fail or do not tolerate nonopioid medications, including the American Pain Society, the American Academy of Pain Management, the American Geriatrics Society (AGS), and the 2011 Institute of Medicine report on "Relieving Pain in America."[95-97] Indeed, the AGS considers opioids as safe as or safer than NSAIDs in older patients with chronic pain. Thus, to exclude veterans from the trial who are already receiving opioids from their PCP would adversely affect generalizability of our trial results and furthermore deviate from VA and non-VA standard of care for chronic pain.

2) Empirically, the selected use of opioids in our VA HSR&D funded trials of chronic pain (Table 2) has been IRB-approved and has not resulted in any serious adverse events. This includes experience with nearly 500 veterans with chronic pain enrolled in our ESCAPE and SCOPE trials. These trials have had opioid use procedures in common with CAMMPS including the requirements for opioid pain care agreements, urine drug screens, regular monitoring, and close collaboration with the veteran's primary care physician. Notably, most participants on opioids in these trials were receiving opioids from their PCP at the time of enrollment in the trial, and the small subset (< 10%) who were initiated on opioids during the trial typically required only low to moderate doses.

Procedures Regarding Opioid Use in CAMMPS

- Opioids will not be initiated by the study team as part of the analgesic algorithm (Figure 5).
- Patients already receiving opioids from their primary care physician (PCP) at the time of study enrollment will receive education about safe use of opioids by the study team, and be regularly monitored for side effects, other adverse events or aberrant drug behavior.
- If pain persists despite proceeding through all 4 steps of the analgesic algorithm, the study team will discuss with the PCP/PACT whether a trial of opioids is warranted. An empiric trial may be considered if all of the following criteria are met:
    - Patient is not at high risk for opioid misuse as determined by an evidence-based classification algorithm we have used in our SCOPE trial (Appendix 1)
    - Patient agrees to an opioid pain care agreement, and regular monitoring for pain response, adverse events, and indicators of misuse
    - Opioid therapy will be considered as an empiric trial and will be discontinued in the event of inadequate pain response, adverse events, or opioid misuse
- Patients receiving any opioids will be educated about adverse events and safety issues (including the use of lockboxes and other security measures to prevent access of others, especially children, to their opioid medications).

D7d. Antidepressant Algorithm for Depression and Anxiety

Our antidepressant algorithm is informed by three recent trials: the landmark multi-center STAR*D trial[98], our SCAMP trial[54], and the algorithm used for anxiety disorders in the CALM trial.[99] STAR*D trial enrolled 4031 patients with major depression who were initiated on an SSRI, of whom 1439 had an inadequate response and proceeded to step 2.[98] Of note, 41% were enrolled and treated in primary care clinics and these patients had outcomes equivalent to those enrolled and treated in psychiatry clinics. Also of note, no specific antidepressant or combination proved superior, but instead the key to optimizing the proportion of patients achieving remission was regular depressive symptom monitoring coupled with dosage escalations or medication/other treatment changes.

Table 6 outlines our general prioritization of antidepressant selection and indications in special circumstances. An SSRI is the first choice because of wide usage, low cost, and well-established efficacy, safety and tolerability.[62,98] Head-to-head trials and a systematic review suggest individual SSRI antidepressants are similar in efficacy and tolerability.[62,100] Sertraline and citalopram are the first-line SSRIs in our algorithm because of their balance of efficacy and tolerability as demonstrated in a recent meta-analysis of antidepressants[101], their favorable profile in terms of drug-drug interactions, their cardiovascular safety in the SADHART and CREATE trials[102,103], and their testing in both the STAR*D and SCAMP trials. In patients who are enrolled with anxiety as one of their PAD disorders, sertraline will be used first because of the greater clinical trial evidence and FDA indications across multiple anxiety disorders. An SNRI will be used in those who fail an SSRI due to evidence from multiple clinical trials of SNRI efficacy in pain and anxiety disorders as well as depression.[104,105]

Should there be a suboptimal response to an SNRI or SSRI, steps 3 through 5 are summarized in Table 6 and adapted from STAR*D and SCAMP. Four key points should be emphasized. First, buproprion has neither strong evidence nor an FDA indication for treatment of anxiety; therefore, it will not be used in patients with anxiety only, and will only be used in combination with an SNRI or SSRI if patients have both depression and anxiety (step 6). Second, the sequence in Table 6 is also evidence-based for PTSD, with VA/DoD guidelines showing significant benefits for SSRIs and SNRIs and some benefit for mirtazapine (*VA/DoD Clinical Practice Guideline: Management of Post-Traumatic Stress, Table I-6, p. 151, 2010*, www.healthquality.va.gov). Third, combination therapy, when considered, will consist of an SSRI or SNRI coupled with one of 3 drugs: buproprion, mirtazapine, or buspirone (i.e., combinations used in STAR*D). Fourth, the CAMMPS algorithm provides a sequence of antidepressant selection that is both rational but at the same time flexible enough to allow appropriate tailoring based upon patient history (i.e., experience with prior antidepressants in terms of response, intolerance, etc.), medical comorbidity (e.g., demonstrated safety of sertraline and citalopram in patients with cardiovascular disease), psychiatric comorbidity (i.e., anxiety), and secondary drug effects that may lead to either preferential selection or avoidance of a particular drug (e.g., the sedation that may occur with mirtazapine may be beneficial in the depressed

patient with insomnia while the risk for weight gain may be undesirable in obese or diabetic patients). See **Appendix 2** for further details on the medication algorithms for depression and anxiety

While Table 6 provides a rational sequence of drug selection, we are not testing any particular antidepressant but, instead, optimal medication management that is both effective and tolerated in an individual patient. Previous research has shown that fewer than half of patients started on a given antidepressant will achieve remission with the first drug.[62,106] This was verified in our SCAMP trial where, of the 100 intervention subjects whose antidepressant status was known at 12 months, only 41% had remained on the antidepressant to which they were initially assigned, 43% had switched to a different antidepressant (n = 38) or combination pharmacotherapy (n = 5), and 16% were on no antidepressant.[42] Thus, our pragmatic, patient-specific approach approximates real-world *in vivo* depression management rather than an inflexible *in vitro* testing of a single drug. At the same time, our algorithm provides a structured approach for the care manager, consistent with the STAR*D[107], SCAMP[54] and CALM[99] effectiveness trials.

For patients already on an antidepressant upon enrollment, adjustments or medication changes will be recommended if, despite antidepressant therapy, they remain clinically depressed and/or anxious. This is a similar approach used in previous effectiveness trials by us and others which have shown that patients in primary care are frequently treated with antidepressants that are either inadequately dosed or ineffective for them. Subjects will be referred to mental health if they fail to achieve an adequate response after trials of 2 different antidepressants, report suicidal ideation, or if they request a referral.

Table 6. Antidepressant Selection and Dosing Details for CAMMPS †

Priority	**Indications**	**Class**	**Drug**	**Dose (in mg)**	
				Initial	**Increases**
1	1st-line (unless anxiety) including CV disease	SSRI	Citalopram	20	30, 40
1	If anxiety or cardiovascular (CV) disease	SSRI	Sertraline	50	100, 150
2	SSRI failure; refractory pain	SNRI	Venlafaxine	75	150, 225
2	SSRI failure, refractory pain	SNRI	Duloxetine	30	60
3	SSRI/SNRI failure; weight gain; sexual side effects	Other	Bupropion	200	300, 400
4	SSRI/SNRI failure; insomnia	Other	Mirtazepine	15	30, 45
5	SSRI failure; refractory pain	TCA	Nortriptyline	25	50, 75
6¶	Partial response to antidep. Monotherapy		Combination ¶		

† Adapted from STAR*D, SCAMP and CALM trials. Further details are provided in Appendix 2.
¶ Acceptable combinations are those used in STAR*D, except lithium or thyroxine will not be used.

D7e. Facilitated Mental Health Care

Patients will be offered an option of psychotropic medications, referral to psychologists embedded in primary care for psychotherapeutic treatment of their depression and/or anxiety, or combined therapy. Those with PTSD will be especially encouraged to accept a psychology referral. Moreover, patients not responding to one treatment will be encouraged to consider combined therapy. Depression (PHQ-9) and anxiety (GAD-7) scores that are obtained by the nurse in response to elevated mood scores derived from automated symptom monitoring will be provided to the treating psychologist as one metric of treatment response and as additional information to determine if additional treatment sessions or modifications to treatment may be warranted. This collaboration between the nurse-physician study team and the embedded primary care psychologists in monitoring and adjusting treatment is one of the innovations of CAMMPS.

D7f. Duration of Intervention

Our 12-month study is divided into 2 phases: (1) acute phase (first 6 months) during which automated symptom monitoring will occur weekly (month 1) and then every other week (months 2 through 6) to allow careful follow-up of symptoms and treatment adjustments; (2) continuation phase (last 6 months) during which automated symptom monitoring will occur once a month for months 7-12 to allow further treatment adjustments in subjects who failed to achieve target clinical responses during the acute phase or to detect

relapse in subjects who did achieve target responses. Automated symptom monitoring will allow nurse care manager contacts to be selective, thereby making 12-month surveillance more efficient.[43]

D7g. Sequencing PAD Symptom Treatment.

Unlike trials aimed at single symptoms, interventions encompassing multiple symptoms must consider whether to approach symptoms simultaneously or sequentially. In general, a sequential approach is preferred for reasons of simplicity and efficiency. It must first be acknowledged there is no evidence-based approach to sequencing symptom treatment in the presence of multiple symptoms. Thus, we provide an operational approach, based upon expected time to symptom improvement, strength of evidence for medications, and the likelihood certain symptoms are secondary to others.

Medication sequencing will be prioritized as: ***pain → depression → anxiety.*** Pain will typically be targeted first since it is probably the most noxious of the 3 symptoms and tends to respond more quickly to medication. There are a number of analgesic options, both short- and long-acting, and some pain improvement is expected to occur in several days to a few weeks if a medication is effective in a particular patient.[88,108] Finally, pain commonly may either trigger or aggravate psychological symptoms.[109,110] Depression and anxiety follow pain in the sequence since their response to treatment may take longer (weeks to several months), and may be moot in the event that pain is ameliorated. Depression is prioritized before anxiety because depression has larger and more pervasive effects on functional status and quality of life.[20,111,112] Moreover, the evidence that primary care based collaborative approaches improve outcomes is much greater for depression than anxiety (35-40 vs. only 2 randomized clinical trials).[28,29,37,38] The 12-month trial duration allows time for sequential treatment in patients.

Occasionally, clinical factors will dictate simultaneous treatment. For example, the person with pain and severe depression might be started on both an analgesic and an antidepressant. Finally, it must be acknowledged that the large number of possible permutations of treatment sequences in a trial enrolling patients with several symptoms will mean CAAMPS is not powered to statistically compare different sequences of symptom treatment, much less specific types or doses of medication. Indeed, this adheres to the principle of ***"treat to target"*** central to a number of symptom effectiveness trials, where the aim is to optimize the clinical outcome with evidence-based treatments rather than to test the efficacy of any particular medication or treatment, singly or in combination.[42,52,113]

D7h. Defining a Clinical Response

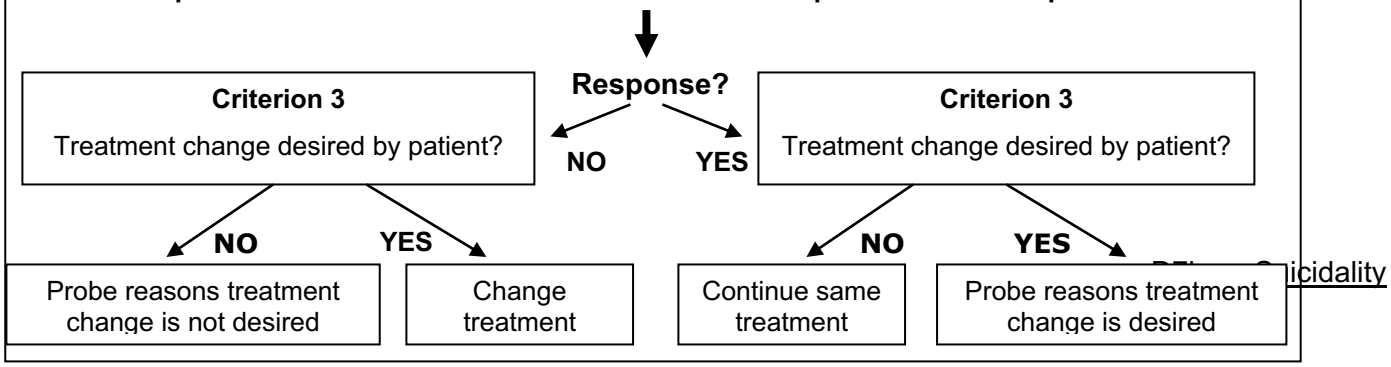
1. Symptom severity measure PEG (pain); PHQ-9 (depression); GAD-7 (anxiety)
2. Global improvement
   "Overall, would you say your pain recently is: (1) Worse; (2) About the same; (3) A little better; (4) Somewhat better; (5) Moderately better; (6) A lot better; (7) Completely better
3. Treatment change desired:
   "Would you like to make some changes in the treatment for your pain?" (Yes or No)

The 3 criteria in **Figure 6** assess the core outcome domains recommended by IMMPACT: pain intensity/interference, patient-rated global improvement; and satisfaction with treatment.[70,114] A ≥ 30% reduction of in pain is a commonly accepted threshold in pain treatment trials and is therefore defined as a partial response (Criterion 1). Criterion 2 represents the patient's assessment of the direction and magnitude of symptom change. A patient's desire for treatment change (Criterion 3) typically represents a clinical action threshold signifying dissatisfaction with the current level of symptom control and a willingness to embrace the costs of and adjustment to increased or added treatments.

The decision to make treatment changes in symptom-based conditions like pain, depression and anxiety cannot be done in a formulaic ("cookbook") fashion because, unlike conditions measured independent of patient-report (e.g., blood pressure, serum glucose, cholesterol), symptoms are self-rated and rely primarily on the patient's internal weighting of symptom severity, interference with valued roles and activities, pros and cons of treatment changes, and other factors unique to the patient. However, the 3 clinical response criteria will be regularly assessed and applied by the nurse-MD symptom team in their weekly case management meetings. Clinical decision making will be guided by the algorithm in Figure 6 in accordance with 7 operating principles outlined in **Appendix 3.**

Figure 6. Algorithm for Using Clinical Criteria to Decide on Treatment Changes

Criterion	Measure	Partial response (4-11 weeks)	Target response (≥ 12 weeks)
1	PEG (pain) PHQ-9 (depression) GAD-7 (anxiety)	≥ 30% decrease	≥ 50% decrease, or score of < 4 on PEG or < 5 on PHQ-9 or GAD-7
2	Global improvement	4 or greater ("somewhat better")	6 or greater ("a lot better")



Subjects who endorse thoughts of self-harm (either spontaneously or by a positive response to item 9 of the PHQ-9) will be assessed with a standardized algorithm that we have used and validated in previous depression trials involving more than 3000 subjects.[115] This validated algorithm (**Appendix 4**) provides a structured interview for the research assistants or nurse care manager that classifies the subject as low to minimal risk (Action Routine) or intermediate or higher risk (Action Today). Although less than 5% of individuals who trigger the algorithm fall into the Action Today category, a physician-investigator is available 24 hours a day 7 days a week to take over management of Action Today subjects. Those classified as Action Today during the eligibility interview will not be enrolled but instead immediately triaged for formal evaluation by a mental health professional in our VAMC.

D7j. Other Safety Concerns and Adverse Events

Patients on an NSAID who are older than 70 or have a history of heart failure, liver disease, diabetes, or concurrent nephrotoxic drugs must have had a creatinine within the past year of initiation and may have a repeat creatinine 4-8 weeks afterwards if clinically indicated. Acetaminophen will be limited to ≤ 2 gm/day in cirrhosis and chronic alcohol use (>3 drinks per day). Tramadol will not be used in patients with a history of seizures. Regarding antidepressants, patients started on and titrated to a dose of a tricyclic antidepressant (TCA) equivalent to 100 mg amitriptyline or 50 mg nortriptyline or 75 mg venlafaxine must have well-controlled blood pressure at baseline, and at recheck within the first 2 weeks. Other monitoring of adverse events is described in the Human Subjects section.

D7k. Other treatments

Subjects will continue to be followed by their primary care physician (PCP) for all medical care not related to the study. Specifically, use of all analgesic and psychotropic medications will be assessed, both to adjust for co-intervention differences between groups in the analyses and to assess as secondary outcomes. For example, a decreased proportion of patients requiring opioids from their PCP would also be an important secondary outcome.

D8. End-of Study Evaluation

Since CAMMPS is a comparative effectiveness rather than implementation trial, the principal analyses will be quantitative rather than mixed-methods. However, we will conduct an evaluation upon completion of the trial to inform subsequent implementation of the ASM and CSM interventions. We have conducted clinician surveys and qualitative interviews as described below in our previous trials which have

proven highly informative.[43,116-119] This qualitative work has been critical to help us understand how patients believed they benefitted (or did not benefit) from an intervention by obtaining patients' perspectives on the relative contribution of each intervention component, and giving us important information about how an intervention can be improved. Our provider surveys have likewise yielded important insights. This is especially critical given the innovative features of this trial.

D8a. Survey of study patients and providers.

All study patients will complete a survey regarding the intervention as part of their 12-month interview. This survey will be a modified version of that used in our INCPAD trial which provided valuable feedback as reported in a recent publication.[43] Similarly, we will develop a similar survey to be administered to participating PCPs and psychologists to elicit their perspectives regarding the interventions.

D8b. Semi-structured interviews involving study participants.

Methods similar to those used in our qualitative evaluations of our SCAMP trial will be used.[116,117] Briefly, those willing to participate will complete written informed consent. Participants will be purposively sampled to maximize diversity in age, gender, and race/ethnicity in an effort to increase the range of comments and perceptions elicited.. Based on previous experience, we anticipate conducting up to 30 semi-structured interviews with research participants. An experienced qualitative researcher and moderator, Dr. Matthias, will lead the study team in completing these interviews , combining open-ended questions with a series of probing questions to elicit perceived barriers and facilitators to key components of the interventions. Audio-tapes of the interviews will be transcribed and checked for accuracy.

D9. Statistical Analysis

D9a. Sample size determination.

Sample size is determined to ensure adequate power for our primary hypothesis in Specific Aim 1, i.e. CSM is superior to ASM in reducing composite PAD symptom severity. In our previous SCAMP and INCPAD effectiveness trials targeting depression and pain in primary care and cancer patients, respectively, the average intervention effect size, compared to a usual care control group, was 0.55 for pain and 0.54 for depression.[42,52] Since CAMMPS will be comparing CSM to an active comparator ASM group rather than a usual care control group, we will conservatively estimate a smaller effect size of 0.35, which is half way between a small effect size of 0.2 and moderate effect size of 0.5.[120] As noted previously, our primary outcome will be a composite pain-anxiety-depression score using the BPI, GAD-7, and PHQ-9 scores, respectively. A standard z-score will be calculated for each scale as follows: subject's scale score minus the sample mean divided by the sample standard deviation.[124] A composite pain-anxiety-depression score will be the average of the standard z-scores for the 3 scales. Since the z-score already is equal to the number of standard deviations, a between-group composite z-score difference of 0.35 is equivalent to an effect size of 0.35. Having 128 participants per treatment arm, we will have 80% power to detect an between-group effect size difference of 0.35 using a two-sample t-test with a 5% Type I error rate. In our previous trials, 12-month attrition has been < 10%. Allowing for 15% attrition in our present trial, we would need 150 per treatment arm, or a total of 300 participants. Because of the use of repeated measurements (see D9b below) and adjustment for baseline characteristics, the error variance of the model is likely to be smaller as compared to unadjusted analyses. As a result, the power is likely to be greater than the nominal level of 80%.

D9b. Analysis for primary aim.

Aim 1. *To compare 12-month effectiveness of CSM vs. ASM in improving overall pain and mental health. Our hypothesis is that CSM will be superior to ASM in reducing a composite pain-anxiety-depression severity score.*

All analyses will be based on intention-to-treat in all randomized participants. Before we perform the group comparisons of intervention effect, we will summarize the patients' baseline characteristics by groups and compare between groups for any indication of systematic differences using two-sample t-tests for continuous variables and Chi-square tests for categorical variables. As the main test of our trial's treatment effect, we will evaluate the ***overall*** between-group differences on the composite pain-anxiety-depression z-score (calculated as described in section D9a) over the 12-month ***period*** of the trial using mixed effects

model repeated measures (MMRM) analysis in a similar way to Kroenke et al.[42,52] Specifically, the composite z-score at 1, 3, 6, and 12 months will be used as the dependent variable in the model. Intervention group and dummy variables indicating the follow up time (1, 3, 6 months, and 12 months) will be included as the main predictors. Baseline composite score will be adjusted. The test of intervention group effect under this model will provide a comparison of the average difference in z-score over the 12 months between the two groups which is our main goal. A random intercept will be used to adjust for within-subject correlation. We will also evaluate the time-specific (1, 3, 6, and 12 months) between-group difference by using the MMRM model with additional interaction terms of time and intervention group. The group difference accompanied with 95% confidence interval will be provided.

Sensitivity analyses for primary outcome. We will use 4 secondary analytic strategies to test the robustness of our main composite z-score outcome. First, we will compare between-group differences on the PROMIS composite T score calculated as described in section D4a. Second, we will calculate a z-score and PROMIS T score for each subject using only their threshold-level symptoms, and compare groups on these patient-specific composite scores. Third, we will compare between-group differences in patient-rated global improvement, a measure that has proved sensitive to intervention effects in our previous trials.[42,52] Fourth, we will compare between-group differences in non-PROMIS symptom measure scores in the subset enrolled with that symptom (i.e., PHQ-9 differences in subset enrolled for depression; GAD-7 differences in subset enrolled for anxiety).

Moderator analyses. We will explore the role of potential baseline moderators (age, sex, race, medical comorbidity, disability index, sociodemographic disadvantage factors [low education, low income, unemployment]), and substance use risk. We will test for interactions between these potential moderators and treatment arm in separate models. A variable will be considered an effect moderator if the coefficient for the interaction term is significant ($p \leq .05$). Since our study is not specifically powered to detect moderator effects, only moderate to large moderator effects are likely to be detected.

D9c. Analyses for Secondary Aims.

Since CAMMPS is not powered for the secondary aims, these results should be interpreted cautiously unless they are highly significant.

Aim 2. *To compare 12-month effectiveness of CSM vs. ASM in improving specific PAD symptoms. Our hypothesis is that CSM will be superior to ASM in reducing pain, anxiety, and depression severity scores individually.*

For these analyses, only the subgroup enrolled for each symptom will be compared. Between-group differences for pain will be tested using all enrolled subjects since pain is a required eligibility criterion for this trial. However, between-group differences for anxiety will only be tested for the enrolled subjects with threshold-level anxiety, and likewise for depression. Each symptom subgroup will be compared on the PROMIS and the non-PROMIS symptom measure. Specifically, between-group differences in pain will be compared on the PROMIS pain measure and the Brief Pain Inventory; between-group differences in the subgroup enrolled with threshold-level anxiety will be compared on the PROMIS anxiety measure and the GAD-7; and between-group differences in the subgroup enrolled with threshold-level depression will be compared on the PROMIS depression measure and the PHQ-9. Similar to the primary analysis, overall between-group differences over the 12-month trial period will be compared using MMRM. The pain, anxiety, or depression score at 1, 3, 6, and 12 months will be used as the dependent variable. Intervention group and time (1, 3, 6, and 12) will be used as the predictors adjusting for the baseline symptom score. For each analysis focusing on a specific symptom subgroup, between-group differences analyses will be adjusted for the severity of each of the other two PAD symptoms. A random intercept will be used to adjust for within-subject correlation. We will also evaluate the time-specific between-group differences by using the MMRM model and provide the 95% confidence intervals.

Aim 3. *To compare the effects of CSM vs. ASM on secondary outcomes, including health-related quality of life, health care utilization, treatment satisfaction, and patient and provider perceptions of barriers and facilitators to CSM and ASM.*

Quantitative Analyses. Most secondary outcomes are continuous variables. For them analytic techniques will be similar to those described under Primary Analysis (section D9b) using MMRM, with the dependent variable in separate models being secondary outcomes that are both clinically important as well

as potentially modifiable by the intervention. These include the SF-12 PCS and MCS scores, Sheehan Disability score, disability days, global improvement, and treatment satisfaction. For the outcomes of health care use (outpatient visits, emergency department visits, and hospitalizations), we will evaluate the between-group differences using the negative binomial model which takes into account potential differences in length of follow up due to early dropout and allows for overdispersion. Intervention group is the main predictor and other covariates will be adjusted as appropriate. For all secondary outcomes,the p-values will be adjusted for multiplicity using the Sidak method:[62,121] where: adjusted p-value = 1 – (1 – unadjusted p-value)$^{\#\ tests}$

Qualitative Analysis of Semi-structured Interview Data. Three members of the research team led by Dr. Matthias will first read each transcript independently to orient to the data and begin grasping overall themes. Second, the team will begin initial coding, in which each researcher independently labels each segment of data. The team will meet weekly to compare and discuss these initial labels, resolving discrepancies iteratively by consensus. The team will use constant comparative methods throughout this process. Once a set of codes is agreed upon and remains stable and consistent across transcripts, the team will move on to focused coding. During focused coding the team will continue to evaluate the adequacy of each code and make any necessary changes by consensus. The team will meet regularly to compare coding and ensure consistency. Coding and analysis will be facilitated by the qualitative data software, ATLAS-ti. Finally, data will be summarized and grouped into conceptual themes and then analyzed using standard qualitative techniques.[122,123]

Aim 4*. To explore the relative contribution of each intervention component to overall symptom improvement. These 5 components are automated symptom monitoring, prompted self-management, nurse contacts, optimized medication changes, and facilitated mental health care. Our hypothesis is that each of these components will have a dose-response relationship with the degree of improvement in the primary outcome.*

This exploratory aim is guided by our Conceptual Model shown previously in Figure 3 and is intended to examine the potential dose-response effect of each of the 5 components summarized in Table 5 (section D6). For this exploratory aim, we will use participants from the CSM arm only since they received all 5 active components. We will quantify the 5 components as follows: 1) automated monitoring contacts (total number); 2) self-management strategies completed (number of self-management units completedby the patient as captured on the automated monitoring website); 3) medication changes (new analgesic and psychotropic starts, dose adjustments, and composite medication changes (summing medication starts and dose changes) with the latter as the principal measure; 4) nurse contacts (total number); 5) mental health visits (total number). The approach to capturing and quantifying these variables will be similar to previous trials by our team as well as others.[46,52] We will run separate linear regression models for each of the 5 components with the 12-month change in our primary outcome (PAD composite score) as the dependent variable and the specific component as the predictor variable adjusting for relevant covariates. A significant coefficient for a specific component will suggest a continuous association between that particular component and the primary outcome. These analyses will allow exploration of a dose-response effect of each component.

D9d. Handling missing data.

All outcome assessments will be interviewer-administered as in our previous trials totaling more than 3000 patients, where missing data at the item level was <1% for individuals completing assessments. Also, among participants alive at each assessment, interview completion rates were high (85-90%]. MMRM is our primary analytic approach and accommodates missing at random without imputations. To check whether the missing status depends on treatment assignment and/or other covariates, we will fit a logistic model with missing status as the outcome and treatment group and other baseline characteristics as covariates. Second, to test the robustness of our MMRM results, we will also run models using 2 imputation strategies (LOCF and multiple imputations). In our 2 recent trials, all 3 strategies yielded similar results.[42,52]

E. PROJECT MANAGEMENT PLAN

E1. Project Timeline

Table 7. CAMMPS Study Timeline																
	Year 1				**Year 2**				**Year 3**				**Year 4**			
Months	**0-3**	**4-6**	**7-9**	**10-12**	**13-15**	**16-18**	**19-21**	**22-24**	**25-27**	**28-30**	**31-33**	**34-36**	**37-39**	**40-42**	**43-45**	**46-48**
Start-up																
Enrollment (10 per mo)																
Intervention & Outcome Assessment																
Analysis																
Reports and Manuscripts																
Dissemin-ation																

As shown in the Study Timeline above (**Table 7**), this is a four-year project. The first 4 months will involve hiring and training personnel. Important steps will include: (1) finalizing the treatment manuals; (2) training the research nurse care manager in assessing pain, depression and anxiety; managing analgesic and antidepressant medication; and delivering the pain and mood self-management program; (3) training the research assistants in the procedures for screening, enrolling, and consenting study subjects, and conducting the telephone-based outcome assessments; (4) working with Interactive Performance Technology (IPT) to set up the automated symptom monitoring program; (4) working with VA data managers to identify potential study subjects from CPRS; (5) obtaining permission from primary care physicians to approach patients of theirs who might be eligible.

During the next 26 months, we will enroll 300 subjects into the clinical trial, which will be approximately 11-12 patients per month or an average of 3 patients per week. Each subject will be followed for 12 months, with outcome assessments at baseline, 1, 3, 6, and 12 months. Thus, patient enrollment will be conducted from months 5-30, and the interventions and outcome assessments will occur during months 5-42. Data analysis will be conducted during the final 16 months of the study (separate baseline and end-of-study analyses), and the main reports and manuscripts will be prepared during the final year. Also, dissemination activities as outlined in the application will commence during the final 12 months.

E2. Overall Project Coordination and Facilities

Overall project coordination will be led by Dr. Kroenke (PI) and Ms. Evans (Project Coordinator). Ms. Evans will coordinate all aspects of the project, trouble-shoot any problems, and provide regular updates on recruitment progress. Drs. Kroenke, Bair, and Matthias have office, meeting and research space within the HSR&D Center for Implementing Evidence-based Practice (CHIC) at the RVAMC. The CHIC 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. Yu's office is within the Health Information Technology Services building, a 5-minute drive from the CHIC.

E3. Investigator and Study Personnel Roles and Responsibilities

Dr. Kroenke will serve as the Principal Investigator and be responsible for the overall conduct of the project and allocation of funds. He will train and oversee the Project Coordinator. He will hire the nurse care manager and the research associates (RAs) and train them in care management duties and administering the outcome battery, respectively. He will serve as Medical Director for the study, supervising the nurse care manager in the weekly case management meetings as well as on an as-needed basis for more immediate decisions. He will oversee patient enrollment, meeting weekly with the RAs to monitor and modify recruitment procedures. He will head the outcome assessment team whose data collection will

remain blinded to the intervention.

Dr. Bair will serve as Associate Medical Director, assisting Dr. Kroenke in his duties. *Dr. Matthias* will lead the qualitative interviewing team and qualitative data analysis.

Dr. Yu will oversee all data analyses including the responsibilities of the masters-level biostatistician. He will direct the interim analyses for the generation of abstracts and will supervise the primary and secondary analyses for manuscripts.

Sharon Weitlauf, BS, RN will serve as the nurse care manager. She will provide medication management according to analgesic and antidepressant algorithms. She will contact patients at scheduled intervals or as triggered by automated symptom monitoring, monitor treatment response and adherence, and coordinate care between the study team, primary care physicians, and the psychologists embedded in primary care. Ms. Weitlauf is the nurse care manager on our VA-funded SCOPE trial.

Jeffrey Barnd, MS, and Jingwei Wu, MS, will serve as the data manager and data analyst, respectively. Together, they will program all study databases, retrieve information from the electronic medical records, assure data integrity and privacy, and conduct all analyses.

Erica Evans will serve as the Project Coordinator. She will oversee all aspects of patient enrollment, supervise the RAs, maintain study files, schedule meetings, manage budgets, and prepare all reports. She will work with the data managers to obtain patient lists, meet weekly with RAs and the investigators to monitor recruitment, retention, delivery of the intervention, and outcome assessment.

Stephanie McCalley will serve as the principal Research Assistant (RA) and will be responsible for recruitment and blinded outcome assessment (baseline and 4 follow-up interviews) of the 300 study subjects. She will also coordinating patient travel and incentives, perform data entry, and other study tasks. She will be assisted in these activities by a student who will serve as a part-time RA. Ms. McCalley has been the RA on our INCPAD and SCOPE trials.

Interactive Performance Technology will: (1) set up the home-based automated symptom monitoring; (2) design and program the IVR calls and voice record prompts; (3) train and support the research team in use of the system; (3) maintain the system for the duration of the study. We have worked effectively with IPT in our INCPAD and SCOPE trials which enrolled Veterans.

E4. Data Management

Data management infrastructure will be provided by the CHIC. All data will be stored in password-protected folders on a secure VA shared drive that is backed up daily. Access to these folders will be limited to authorized study personnel. Outcome assessments will be programmed on a VA shared drive using Microsoft Access and research assistants will enter data into the database after conducting interviews. Algorithms will be created to check for inappropriate or missed data entry, to score the questionnaires and store the summary scales within the database, and to determine the appropriate date for follow-up interviews. Identifying information will be restricted to approved study personnel. A study identification number will be created and the document linking it to identifying information will be kept in a password-protected access-limited folder on the secured drive. The study identification number will be used for data analysis and other purposes to protect patient confidentiality. Data will be backed up daily onto a secured server at Roudebush VAMC.

F. DISSEMINATION PLAN

(1) The VHA National Pain Management Strategy Coordinating Committee, on which Dr. Bair is a core member, will serve as one primary channel for disseminating study findings to VA providers, administrators, researchers and policy makers. Findings will be disseminated to the committee in the form of summary reports and presentations at their annual face-to-face meeting. The Committee will advise and coordinate next steps for dissemination, including dissemination to other relevant entities such as VISN and hospital administrators; local Pain Management Committees; the VISN Pain Points of Contact, the Office of Quality and Performance; and the national working groups related to pain management education, guideline development, and performance measures. Additionally, a summary of study findings and implications will be posted on the VHA Pain Management Committee's website in a format readable to Veterans.

(2) Findings will be disseminated to our research audiences through scientific presentations and publications, and HSR&D cyber seminars, as well as through conference calls with the Pain Research

Working Group, a subcommittee of the VHA National Pain Management Strategy Coordinating Committee. We also will seek synergistic opportunities with the Pain Research, Informatics, Medical comorbidities and Education (PRIME) Center and HSR&D-funded studies on pain management.

(3) Other resources include a a widely subscribed VA pain list serve; a VA national pain management website (www.va.gov/PAINMANAGEMENT/index.asp); monthly national educational teleconferences targeting providers and administrators; a network of VISN Pain Points of Contact who hold monthly teleconferences and who serve an important liaison role between the National Pain Management Committee and facility level pain committees; and a network of VA and non-VA pain-relevant investigators (the Pain Research Working Group) who hold twice monthly teleconferences and yearly face-to-face meetings and who, among their goals, work to promote dissemination of research findings and to influence practice and policy related to pain care. In sum, an established network of resources is already in place to disseminate study findings.

(4) In addition, to the local, regional, and national pain groups we are already tied into, we will disseminate study findings to the Mental Health and Substance Use Disorder QUERI groups, the National Serious Mental Illness Treatment Research and Evaluation Center (SMITREC), the Mental Illness Research, Education, and Clinical Center (MIRECC), and the HSR&D Center for Information Dissemination and Education Resources (CIDER). Our research group has disseminated study findings in the VA HSR&D Cyber-seminar forum sponsored by CIDER.

(5) Papers published in peer-reviewed journals are an important source of disseminating research results. Our productivity in this regard has been strong: our 2 recently-completed trials (SCAMP and INCPAD) have resulted in 15 and 12 publications to date, respectively. Examples of some projected papers from CAMMPS are outlined in **Table 8** below.

Table 8. Selected Proposed Paper from CAMMPS Trial

1	CAMMPS trial design (methods) paper	6	Intervention mediators and moderators
2	Pain-anxiety-depression triad (baseline data)	7	Provider and patient survey results
3	Main trial results paper – 12 month outcomes	8	Patient semi-structured interview results (patients)
4	Predictors of 12-mo pain outcomes	9	PROMIS vs. non-PROMIS symptom measures
5	Predictors of 12-mo depression/anxiety outcomes	10	Somatization and stress

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HUMAN SUBJECTS PROTECTION

1. Overview

The target population for this Comprehensive vs. Assisted Management of Mood and Pain Symptoms (CAMMPS) study will be veterans receiving care at one of the Roudebush VAMC primary care clinics or VA Community-Based Outreach Clinics (CBOCs) and who suffer from clinically significant levels of chronic pain, anxiety, and/or depression (i.e., PAD conditions). Veteran patients in primary care who meet clinical severity levels of pain plus comorbid depression and/or anxiety as well as other eligibility criteria and who provide informed consent will be randomized to one of two treatment arms. One group will receive *assisted symptom management* (ASM) by interactive voice recording or Internet with prompted pain and mood self-management. The second group will receive *comprehensive symptom management* (CSM) which combines ASM with centralized medication management delivered by a nurse-physician specialist team, care coordination, and facilitated mental health care. Both interventions will be enhancements to standard primary care. Research assessments, consisting of self-administered questionnaires and standardized interviews, will be conducted at baseline, 1, 3, 6, and 12 months. The evaluation instruments are validated measures to assess pain, anxiety, depression, health-related quality of life, and other patient-reported variables that can be effectively administered by trained research assistants. In short, CAMMPS compares: 1) usual care *plus* assisted symptom management (ASM) vs. 2) usual care *plus* ASM *plus* optimized medication management and facilitated mental health care(CSM).

2. Risk to Subjects

2a. Human Subjects Involvement and Characteristics

All Veterans 18 years and older will be potentially eligible. All subjects recruited for the study will be Veterans. A total of 300 subjects will enrolled. Veterans receiving care in one of the Roudebush VAMC primary care clinics or VA CBOCs will be eligible if they have comorbid pain plus anxiety and/or depression.

Pain must: (a) be musculoskeletal, either localized (in the arms, legs, back, or neck) or widespread (fibromyalgia); (b) have persisted 3 months or longer despite a trial of at least one analgesic medication; (c) be at least moderate in severity, defined as a Brief Pain Inventory average severity score of 5 or greater. *Depression* must be of at least moderate severity, defined as a PHQ-8 score ≥ 10 with either depressed mood and/or anhedonia being endorsed. *Anxiety* must be of at least moderate severity, defined as a GAD-7 score ≥ 10 or greater.

Excluded will be individuals who: (a) do not speak English; (b) have moderately severe cognitive impairment as defined by a validated 6-item cognitive screener; (c) have schizophrenia, bipolar disorder or other psychosis; (d) are suffering from a complex or severe mental illness or are at high risk of suicide as their condition is unsuitable for a predominantly telecare intervention; (e) are pregnant; (f) have an anticipated life expectancy of less than 12 months.

This trial does *not* involve special vulnerable populations, such as fetuses, neonates, pregnant women, children less than 18 years old, prisoners, institutionalized individuals, or others who may be considered vulnerable populations.

2b. Sources of Materials

The research material that will be obtained from study participants will be primarily data provided by them during research interviews or excerpted from their medical records (CPRS). Participants in the CSM arm in whom a nonsteroidal anti-inflammatory medication is started

during the study or in whom opioid medications are started or increased may be asked to provide a blood test (for serum creatinine) or a urine test (for drug testing) as part of clinical care. All data gathered from participants will be with their approval as documented by written informed consent and HIPPA authorization.

The data gathered will be obtained during research interviews and focus on the severity of pain, anxiety and depression as well as health-related quality of life, symptom-related treatments, health care use, and sociodemographic information. The exact patient-reported measures to be used are described in the Research Plan.

Only study team members (study investigators, project coordinator, research assistants, nurse care managers, data managers, biostatisticians) who are IRB-approved will have access to individually identifiable private information. Measures to assure privacy and confidentiality are described in Section 2dii(2) below.

2c. Potential Risks

Potential risks primarily involve direct adverse effects of FDA-approved medications which are well-described and minimal in most patients. Side effects of these medications typically resolve shortly after stopping them. Since patients will also have depression and/or anxiety, another potential risk is emotional distress related to the discussion of psychological symptoms; this is typically a minor issue and well handled by trained research interviewers and study nurse care managers. Some patients may have a small amount (two teaspoons) of blood drawn before or starting a study medication which could result in some discomfort or bruising where the blood was drawn or the needle was placed. Suicide is an exceptionally rare event in medical patients enrolled in trials, and safeguards are discussed in section 5ciii below.

Alternative treatments for potential study participants include receiving standard care from their primary care physician for their pain, anxiety and/or depression, receiving care from a mental health specialist, or receiving no treatment. The risks (failure of symptoms to improve) and benefits (symptomatic improvement) of these alternative treatments will be explained during the informed consent procedure.

2d. Adequacy of Protection against Risks

2di. *Recruitment and Informed Consent*

Primary care physicians (PCPs) will be informed of the study in detail and provide written consent to approach their patients for participation in the trial. Only patients from consenting PCPs will be enrolled. Electronic medical records (CPRS) will be used to create a master list of individuals who, within the preceding 36 months, have received an ICD diagnosis of a depressive disorder, an anxiety disorder, or a musculoskeletal pain condition. This patient list will be updated quarterly during the enrollment period. Individuals on this list will be mailed a letter describing the study and contacted within 2 weeks by telephone to determine potential interest in the study and, if willing, complete an eligibility interview.

Eligible patients will be scheduled for an in-person research visit where written informed consent and HIPPA authorization will be obtained by the project coordinator or trained research assistants. This consent will be obtained prior to any baseline assessment, randomization, or other study procedures.

2dii. *Protection against Risk.*

1) Patient Safety. No experimental medications will be used in this trial. Rather, we will use analgesics and antidepressants which are FDA-approved for treatment of pain, depression, and anxiety and widely-used in clinical practice. Clinical response to medications as well as any side effects will be monitored by the research nurse/supervising physician-investigator team. For patients who do not tolerate the side effects, the medication will be discontinued and an alternative medication begun in its place. We will use careful evaluation of all subjects at

baseline and close follow-up by a nurse specially trained for this study similar to nurse care managers we have used in our several previous trials.

Women of child-bearing age who are randomized to the comprehensive symptom management (CSM) group will be counseled about appropriate contraceptive measures to use during the time they are on antidepressant medication, consistent with standard clinical practice. Also, in these women, the initial drug of choice will be an SSRI (excluding paroxetine) since safety in the event of pregnancy has been established for SSRIs.

Patients enrolled in this study will have depression and/or anxiety. Also, the outcome assessments include the PHQ-9 depression measure which includes a question about thoughts of self-harm. The procedure for assessing risk of self-harm is discussed in section 5ciii below.

2) Participant Privacy and Confidentiality. We will assure the privacy of the content of all interviews and other data collected as part of this study by assigning patients unique identifiers to track their individual data (rather than using names or hospital or social security numbers) and keep all records under lock with access only by study personnel. Additionally, our IRB consent forms include a HIPPA authorization form that subjects must read and sign prior to study enrollment. All data will be stored in password-protected folders on a secure VA shared drive that is backed up daily. Access to these folders will be limited to authorized study personnel. Identifying information will be restricted to approved study personnel. A study identification number will be created and the document linking it to identifying information will be kept in a password-protected access-limited folder on the secured drive. The study identification number will be used for data analysis and other purposes to protect patient confidentiality. Data will be backed up daily onto a secured server at Roudebush VAMC.

Automated symptom monitoring will be hosted by Interactive Performance Technologies (IPT) which has successfully set up and maintained similar automated monitoring for 202 cancer patients in our recently-completed NCI-funded Indiana Cancer Pain and Depression (INCPAD) trial. IPT also has set up automated monitoring for telecare management of chronic pain in primary care as a component of our VA HSR&D-funded SCOPE clinical trial of collaborative care for chronic pain in Veterans. The research team will access IPT's hosted Symptom Monitor using standard PCs with an Internet connection. IPT's application is fully HIPAA compliant, using secure sockets layer (SSL) technology to authenticate users and encrypt information transmitted over the web. In any instance where data is transferred via non-secure electronic networks, data will be encrypted at the source. Data stored in IVR/CATI databases will be transferred in an encrypted fashion at regular intervals and loaded into a secured central database at IU. Delivery of the intervention will include symptom monitoring via these secure mechanisms and, in the comprehensive symptom management group, involvement of the study participant's primary care physician, psychologist, and the study team consisting of the nurse care manager and the supervising physician symptom specialist. Thus, all exchanges of clinical information will comply with HIPPA standards of patient privacy, and all data collected, transferred, and stored for research purposes will be done in a manner to assure confidentiality.

3) Adverse Event Collection and Reporting. See sections 5d, 5e, and 5f below.

3. Potential Benefits of Research to Subjects and Others

Both study arms are enhancements to the usual primary care provided to Veterans for pain, anxiety and depression. Thus, subjects randomized to either the comprehensive or assisted symptom management arms may experience improvement in their pain, anxiety and depression symptoms typically experience by patients only receiving usual primary care. Given the prevalence of pain, anxiety and depression in Veterans, the benefits of developing and testing effective interventions are substantial.

Study participants will not be charged for any of the study-related calls, including those from the nurse, research assistants, or project coordinator. Likewise, the automated home-

based symptom monitoring done by IVR or Internet will be conducted at no cost. Furthermore, study participants will be compensated $25 for each of the five research assessments conducted at baseline, 1, 3, 6, and 12 months. Participants will be financially responsible for all health care costs not directly associated with this study such as their routine clinic visits, medications, hospitalizations, and other health care.

4. Importance of the Knowledge to be Gained.

Pain, anxiety and depression afflict large numbers of Veterans (as well as non-Veteran primary care patients) and leads to huge individual and societal costs in terms of quality of life, social and work functioning, health care use, and lost productivity. Knowledge regarding the effectiveness of our two systems-based interventions has considerable potential for improving the health of Veterans and the public.

5. Data and Safety Monitoring Plan

Core elements of the following multi-component Data and Safety Monitoring Plan have been successfully used in our 3 previous NIH-funded comparative effectiveness trials as well as our VA-funded ESCAPE and SCOPE trials of pain and depression.

5a. Determination of Level of Risk. This study involves low to moderate risk: It is unlikely that serious adverse events will occur during the study.

5b. Data and Safety Monitoring Board.

We will establish a local Data Safety Monitoring Board (DSMB) that meets every 6 months during the study. Members will consist of individuals not part of the study team and will include a pain specialist, a psychiatrist, a clinical psychologist, a nurse with expertise with care management, and a biostatistician. This DSMB will review adverse events, recruitment, and other data or study procedures as requested. A copy of the DSMB minutes and recommend-ations will be provided to the study PI and will be available to the IRB upon request.

5c. Study Monitoring.

5ci. *Weekly Case Management Review*. The study nurse care manager meets weekly with the supervising physician specialist to review all new patients enrolled in the comprehensive symptom management arm as well as previously enrolled patients who have clinical issues warranting discussion for potential treatment actions or study-related problems. Medication management as well as any side effects or patient concerns are reviewed and discussed. The study PI or back-up physician is available by telephone and/or pager at all times.

5cii. *Monthly Research Team Meetings*. The PI, Project Coordinator, research assistants, nurse care manager, and relevant co-investigators meet monthly for study operations meetings. These meetings will focus on monitoring recruitment, enrollment and dropouts, eligibility, adherence to study protocols, data collection, and adverse events. Minutes of these meetings will be maintained by the Project Coordinator. Reporting of any unusual events or problematic issues will be done by the study PI and/or Project Coordinator. Decisions will be made jointly and recorded in the minutes.

5ciii. *Suicidal risk assessment*. During nurse care manager contacts with subjects in the comprehensive symptom management arm, and outcome assessments by the research assistants with all subjects, the depression measure includes an item asking about “thoughts of death or harming yourself.” If a subject endorses this item at any level, the research nurse or RA proceeds to a scripted interview. Based on the subject’s responses, they are characterized as: Action Routine (low to minimal suicidal risk) or Action Today (higher risk). For Action Today subjects, the investigator on call (PI, Co-PI, or backup physician) is contacted, notified of subject

responses, and directs study personnel how to proceed. Our approach is based upon an evidence-based algorithm that has been validated in our earlier depression effectiveness trials in medical patients (***Appendix 4***). By this algorithm patients are classified as minimal, lower, or higher risk. The latter constitute < 2% of patients enrolled in depression trials, and we have a protocol for expedited evaluation by a study physician for the rare patient in the higher risk group. All research personnel will be trained by the PI (Dr. Kroenke) in this protocol.

5d, Adverse Event Grading.

- The nature and severity of the adverse event as well as study team actions and follow-up of the AE to its resolution will be documented in detail by the study nurse.
- The relationship of the adverse event to the study intervention will be classified in a binary fashion as either probably or possibly study-related or unlikely to be study-related:
- The relationship of the adverse event to the therapy/study will be determined based upon clinical review of all data and subsequent clinical judgment.

5e. Explicit Definition of a Serious Adverse Event (SAE). SAEs include the following:

- Death
- A life-threatening experience
- Inpatient hospitalization
- Prolongation of hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly
- Birth defect
- May require medical, surgical, behavioral, social or other intervention to prevent one of the above outcomes.

5f. Adverse Event Reporting.

- All Serious Adverse Events will be evaluated to see if they meet the 4 criteria that mandate prompt reporting to the IRB (unexpected; related to the study intervention; causing harm or increased risk of harm; and requiring a change to the informed consent statement). Because this is a VA study, however, all SAEs will be reported to the IRB within5 working days using their Prompt Reporting Form, regardless of whether they meet these 4 prompt-reporting criteria.
- All other adverse events will be reported annually with the continuing review.
- All adverse events will be reviewed and evaluated by the Principal investigator.

5g. Specific information evaluated at the time of each DSMB review.

- Recruitment, accrual and dropout statistics, number and description of any AE or SAE, any other additional concerns.
- Data collection – key issues
- A table with the number of adverse events and their severity will be used in the DSMB reports to assess the level of risk/toxicity that occurred.
- The content and format of reporting may be modified as requested by the DSMB members. Since this is an effectiveness trial using treatments proven safe, there are no preplanned interim analyses. However, such analyses including testing of AE rates between groups will be done if requested by the DSMB.

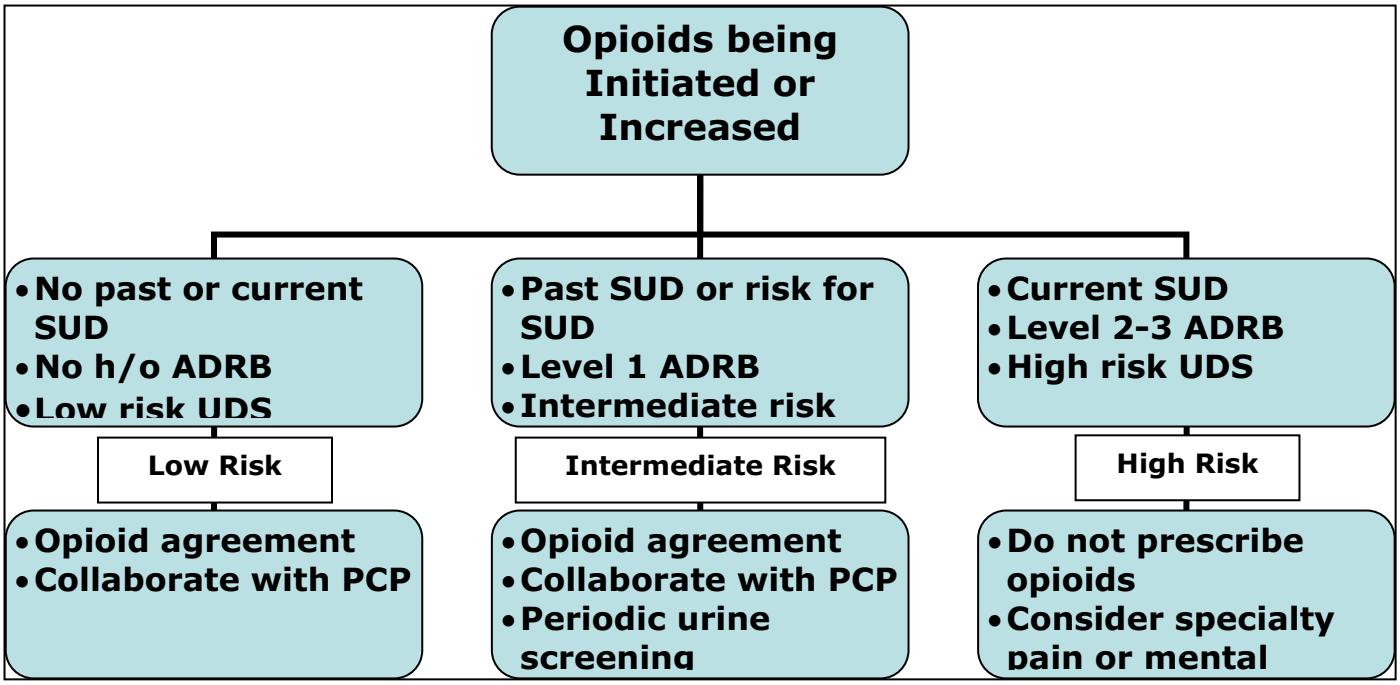
CAMMPS Appendices

Appendix	Item
1	Opioid Risk Stratification Algorithm
2	Medication Algorithms for Depression and Anxietey
3	Key Operating Principles Regarding Analgesic Management
4	Suicidal Ideation Assessment Algorithm

APPENDIX 1

Algorithm for Opioid Misuse Risk Stratification and Clinical Management

Risk assessment for opioid prescribing in CAMMPS will be based on three sources of information, the substance use interview, medical history review, and baseline urine drug testing. Positive screens (interview, history, or urine) will be followed by additional data collection, including a structured substance use interview, to clarify risk categorization. The algorithm is illustrated in the Figure below and described in the subsequent text.



A. Substance use interview

Risk assessment is based on the AUDIT-C and drug history questions, as follows:

1. AUDIT-C score
    a. Low risk: 0-3 (negative)
    b. ≥ 4 is a "positive screen" that should be followed with additional questions
        i. Low risk: No heavy drinking (defined as >14 drinks per week or ≥ 5 drinks/day at least monthly) or abuse/dependence
        ii. Intermediate risk: Heavy drinking without abuse/dependence
        iii. High risk: Probable alcohol abuse/dependence
2. Drug history questions
    a. Low risk: SUB8-10=0-1 and SUB12-13=0
    b. Intermediate risk: SUB8 or SUB10=2 or SUB 9=2-4 or SUB12=1 or SUB13=1
    c. High risk: SUB8 or SUB10=3-4

B. Medical history review

Risk assessment is based on review of CPRS and communication with the patient's PCP.

1. Substance use disorder
    a. Low risk: No past or current known or suspected SUD
    b. Intermediate risk: Remote personal history of SUD or recent (within 2 years) personal history of SUD in remission
    c. High risk: Known or suspected active SUD
2. Aberrant drug related behaviors (ADRB)
    a. Low risk: No history of non-adherence to pain management plans
    b. Intermediate risk: Level 1 behaviors (infrequent minor variations from pain treatment plan, such as requests for early refills, misplacing medications, or minor lending or borrowing of medications from family members)
    c. High risk: Level 2 (frequent, persistent deviations from the treatment agreement or behaviors that are manifestations of addiction or psychiatric or cognitive dysfunction) or Level 3 (serious illegal, criminal, or dangerous behaviors such as diversion or intentional overdose) ADRB.

C. Baseline urine drug testing

Risk assessment is based on urine drug screen (UDS) alone if patient has no current opioid prescription or UDS + opiate confirmation if patient is already receiving opioid medications. Unexpected UDS results will be evaluated with consideration of potential causes for false positives/negatives, repeat testing or confirmation, or toxicology consultation as indicated.

1. If no current opioid medication
    a. Low risk: Negative UDS
    b. Intermediate risk: UDS positive for cannabinoids only
    c. High risk: UDS positive for non-prescribed medication or illicit drugs other than cannabinoids
2. If current prescribed opioid medication
    a. Low risk: Negative for non-prescribed medication or illicit drugs other than cannabinoids AND positive for prescribed medication
    b. Intermediate risk: Negative for non-prescribed medication or illicit drugs other than cannabinoids and negative for prescribed medication (especially in setting of intermittent or low dose opioids that may not be detected)
    c. High risk: Positive for non-prescribed medication or illicit drugs other than cannabinoids, repeated or confirmed negative for prescribed medication (especially round-the-clock or high dose opioids that should be detected)

APPENDIX 2

Medication Guidelines for Depression and Anxiety in CAMMPS

Condition/Medication	Evidence
Depression/Antidepressants	INCPAD trial[A,B], SCAMP trial[C,D], and STAR*D trial[E]
Anxiety/Anxiolytics	CALM trial[F,G], NICE guidelines[H]

A. Kroenke K, Theobald D, Norton K, Sanders R, Schlundt S, McCalley S, Harvey P, Iseminger K, Morrison G, Carpenter JS, Stubbs D, Jacks R, Carney-Doebbeling C, Wu J, Tu W. Indiana Cancer Pain and Depression (INCPAD) Trial: design of a telecare management intervention for cancer-related symptoms and baseline characteristics of enrolled participants. *Gen Hosp Psychiatry.* 2009;31:240-253.

B. Kroenke K, Theobald D, Wu J, Norton K, Morrison G, Carpenter J, Tu W. Effect of telecare management on pain and depression in patients with cancer: a randomized trial. *JAMA.* 2010;304:163-171.

C. Kroenke K, Bair M, Damush T, Hoke S, Nicholas G, Kempf C, Huffman M, Wu J, Sutherland J. Stepped Care for Affective Disorders and Musculoskeletal Pain (SCAMP) study Design and practical implications of an intervention for comorbid pain and depression. *Gen Hosp Psychiatry.* 2007;29:506-517.

D. Kroenke K, Bair MJ, Damush TM, Wu J, Hoke S, Sutherland J, Tu W. Optimized antidepressant therapy and pain self-management in primary care patients with depression and musculoskeletal pain: a randomized controlled trial. *JAMA.* 2009;301:2099-2110.

E. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163:1905-1917.

F. Roy-Byrne P, Veitengruber JP, Bystritsky A, Edlund MJ, Sullivan G, Craske MG, Welch SS, Rose R, Stein MB. Brief intervention for anxiety in primary care patients. *J Am Board Fam Med.* 2009;22:175-186.

G. Roy-Byrne P, Craske MG, Sullivan G, Rose RD, Edlund MJ, Lang AJ, Bystritsky A, Welch SS, Chavira DA, Golinelli D, Campbell-Sills L, Sherbourne CD, Stein MB. Delivery of evidence-based treatment for multiple anxiety disorders in primary care: a randomized controlled trial. JAMA. 2010;303(19):1921-1928

H. McIntosh A, Cohen A, Turnbull N, Esmonde L, Dennis P, Eatock J, Feetam C, Hague J, Hughes I, Kelly J, Kosky N, Lear G, Owens L, Ratcliffe J, Salkovskis P (2004) *Clinical Guidelines and Evidence Review for Panic Disorder and Generalised Anxiety Disorder* Sheffield: University of Sheffield/London: National Collaborating Centre for Primary Care

Antidepressant Guidelines

OVERVIEW

Mandatory Care Manager Phone calls or contacts

Baseline:	Discuss depressive/anxiety symptoms, past treatment history, and treatment options Initiate treatment incorporating patient preferences and treatment algorithms	
Week 1:	Scheduled phone call	(assess side effects and adherence)
Week 4:	Scheduled phone call	(assess response, adjust dose, possibly change med)
Week 12:	Scheduled phone call	(assess response, adjust does, possibly change med)

Triggered Care Manager Phone calls

Care manager calls will be triggered based upon automated symptom monitoring (ASM), either:

- Worsening in depressive or anxiety score (or failure to improve according to guidelines)
- Nonadherence reported on ASM call
- Side effects reported on ASM call
- Patient requests care manager phone contact on ASM call
- Missed ASM reports

GENERAL PRINCIPLES

- Pre-existing antidepressants.
  - If patient is already on an antidepressant at baseline and recently started (past 8 weeks), we may consider increasing the dose of that antidepressant, but discuss with MD investigator first.
  - If patient is on a low-dose antidepressant for a condition other than depression (e.g., peripheral neuropathic pain, fibromyalgia, insomnia, etc.), we may consider continuing that medication while still starting a study antidepressant. The most common examples of this would be low dose amitriptyline or nortriptyline (e.g., 25 mg hs), or trazodone (e.g., 25-100 mg hs).

- If significant side effects limit increasing any study antidepressant and the patient has not had an adequate response, consult study physician for a recommendation.

- PHQ-9 or GAD-7 Targets: General guidelines.
  - Week 4 5 points or greater decrease
  - Week 8 Either a 50% decrease from baseline PHQ-9 (or GAD-7), or an absolute PHQ-9 (or GAD-7) score < 10.
  - Week 12 Either a 50% decrease from baseline PHQ-9 (or GAD-7), or an absolute PHQ-9 (or GAD-7) score < 5

- Antidepressant selection.
  - On first phone call, determine past treatment history for depression.
  - Follow algorithm order, skipping over antidepressants that have failed for the patient
  - Antidepressants will typically be prescribed by the primary care physician or psychiatrist caring for the patient, and guidelines on next pages apply to recommendations we may provide.

- Mental health referral. If monotherapy options exhausted in this set of algorithms – due to past or current antidepressant failures, side effects, or contraindications, facilitate mental health referral.

Antidepressant Selection and Dosing Details for CAMMPS †					
Priority	**Indications**	**Class**	**Drug**	**Dose (in mg)**	
				Initial	**Increases**
1	1st-line (unless anxiety) including CV disease	SSRI	Citalopram	20	30, 40
1	If anxiety or cardiovascular (CV) disease	SSRI	Sertraline	50	100, 150
2	SSRI failure; refractory pain	SNRI	Venlafaxine	75	150, 225
2	SSRI failure, refractory pain	SNRI	Duloxetine	30	60
3	SSRI/SNRI failure; weight gain; sexual side effects	Other	Bupropion	200	300, 400
4	SSRI/SNRI failure; insomnia	Other	Mirtazepine	15	30, 45
5	SSRI failure; refractory pain	TCA	Nortriptyline	25	50, 75
6¶	Partial response to antidep. Monotherapy		Combination ¶		

† Adapted from STAR*D, SCAMP and CALM trials. Further details are provided in **Appendix 4**.

¶ Acceptable combinations are those used in STAR*D, except will not use lithium or thyroxine.

ALGORITHM 1. CITALOPRAM

1. Day 0: Start citalopram, 20mg per day.
2. Week 1: Call patient, assess for adherence and side effects.
3. Week 4: Assess PHQ-9, side effects. If inadequate response, increase to 40 mg per day.
4. Week 8: Assess PHQ-9, side effects. If inadequate response, consider increase to 60mg per day or switch to different antidepressant.
5. Week 12: Assess PHQ-9, side effects; if inadequate response, consider alternative antidepressant.
6. Month 6: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
7. Month 9: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
8. Weaning off citalopram. If a medication change is needed do not stop citalopram abruptly. Decrease to half the patient's usual dose for 5 days, then discontinue. You may start the new medication while weaning the citalopram.

ALGORITHM 1. SERTRALINE

1. Day 0: Start sertraline, 50 mg per day.
2. Week 1: Call patient, assess for adherence and side effects.
3. Week 4: Assess PHQ-9, side effects. If inadequate response, increase to 100 mg per day.
4. Week 8: Assess PHQ-9, side effects. If inadequate response, increase to 150 mg per day
5. Week 12: Assess PHQ-9, side effects; if no decrease or patient subjectively reports no improvement, consider alternative antidepressant.
6. Month 6: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
7. Month 9: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants

8. Weaning off sertraline. If a medication change is needed do not stop sertraline abruptly. Decrease to half the patient's usual dose for 5 days then discontinue. You may start the new medication while weaning the sertraline.

ALGORITHM 2A. VENLAFAXINE SA

Screening and Monitoring Considerations for venlafaxine SA

1. Does the patient have poorly controlled blood pressure (systolic ≥ 170 or diastolic ≥ 100) at baseline; if so consider another agent.
2. Does the patient have cardiac disease (history of myocardial infarction, angina, congestive heart failure, arrhythmia, or other heart disease). If so, consider sertraline or another agent.
3. BP assessment. BP assessed and recorded at study entry (baseline). BP rechecked within the first 1-2 weeks. If systolic BP increases ≥ 20 above baseline (or diastolic increases ≥ 10 above baseline), notify RN who in turn will discuss with physician.

Venlafaxine SA algorithm

1. Day 0: Start venlafaxine SA 37.5 mg qd.
2. Week 1: Assess side effects and adherence. Increase to 75 mg qd. Ask patient to get blood pressure checked by week 4 call (e.g., at pharmacy, supermarket, at home, doctor's office, etc.). Have patient call RN back if blood pressure is elevated (> 170 systolic or > 100 diastolic)
3. Week 4: Assess PHQ-9, side effects; if inadequate response, increase to 150 mg qd. If patient has not had BP checked by week 4 call, ask if there are any barriers to having it checked, and do a follow-up call 1 week later to ask about blood pressure. If patient has still not had blood pressure check, consider bringing patient in for BP check if history of hypertension or if having symptoms (e.g., headache, dizziness, etc.). Otherwise, make sure there is a BP check by week 8.
4. Week 8: Assess PHQ-9, side effects; if inadequate response, increase to 225 mg qd. Also, recommend follow-up blood pressure, if dose increased to 225 mg.
5. Week 12: Assess PHQ-9, side effects; if inadequate response, consider alternative antidepressant.
6. Month 6: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
7. Month 9: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
8. Weaning off venlafaxine. If a medication change is needed do not stop venlafaxine abruptly. Decrease to half the patient's usual dose every 2 days until total daily dose is 75 mg or less, then discontinue. You may start the new antidepressant while weaning the venlafaxine.

ALGORITHM 2A. DULOXETINE

Screening considerations for duloxetine

1. Does the patient have liver disease? If so, choose another antidepressant.

Duloxetine algorithm

1. Day 0: Start duloxetine, 30 mg per day.
2. Week 1: Call patient, assess for adherence and side effects.
3. Week 6: Assess PHQ-9, side effects. If inadequate response, increase to 60 mg per day.

4. Week 12: Assess PHQ-9, side effects. If inadequate response, consider switch to different antidepressant.
5. Month 6: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
6. Month 9: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
7. Weaning off duloxetine. If a medication change is needed do not stop duloxetine abruptly. Decrease to half the patient's usual dose for 5 days, then discontinue. You may start the new medication while weaning the duloxetine

ALGORITHM 3. BUPROPION SA

Screening considerations for bupropion SA

1. Does the patient have a history of seizures or an eating disorder? If so, choose another antidepressant.

Buproprion algorithm

1. Day 0: Start bupropion, 150 mg qd.
2. Week 1: Call patient, assess for adherence and side effects
3. Week 4: Assess PHQ-9, side effects. If inadequate response, increase to 150 mg BID.
4. Week 8: Assess PHQ-9, side effects. If inadequate response, increase to 200 mg BID or consider alternative antidepressant.
5. Week 12: Assess PHQ-9, side effects; if inadequate response, consider alternative antidepressant.
6. Month 6: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
7. Month 9: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
8. Weaning off buproprion. If a medication change is needed do not stop bupropion abruptly. Decrease to half the patient's usual dose for 5 days then discontinue. You may start the new medication while weaning the bupropion.

ALGORITHM 4. MIRTAZAPINE

1. Day 0: Start mirtazapine, 15 mg per day at bedtime.
2. Week 1: Call patient, assess for adherence and side effects..
3. Week 4: Assess PHQ-9, side effects. If inadequate response, increase to 30 mg per day.
4. Week 8: Assess PHQ-9, side effects. If inadequate response, increase to 45 mg per day or consider alternative antidepressant.
5. Week 12: Assess PHQ-9, side effects; if inadequate response, consider alternative antidepressant.
6. Month 6: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
7. Month 9: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
8. Weaning off mirtazapine. If a medication change is needed do not stop mirtazapine abruptly. Decrease to half the patient's usual dose for 5 days then discontinue. You may start the new medication while weaning the mirtazapine.

ALGORITHM 5. NORTRIPTYLINE

Screening Considerations for nortriptyline

1. Does patient have prior history (either documented in medical records or by the patient) of non-response or significant adverse effects with nortriptyline? If so, move to different antidepressant.
2. Does the patient have poorly controlled blood pressure (systolic ≥ 170 or diastolic ≥ 100) at baseline; if so consider fluoxetine or another agent.
3. Does the patient have cardiac disease (history of myocardial infarction, angina, congestive heart failure, arrhythmia, or other heart disease). If so, consider sertraline, citalopram, or another agent.
4. Is an electrocardiogram (ECG) required? It is required in patients who have not had an ECG in the past 3 months. Review an ECG completed in past 3 months with MD investigator.
5. BP assessment. BP assessed and recorded at study entry (baseline). BP rechecked within the first 1-2 weeks. If systolic BP increases ≥ 20 above baseline (or diastolic increases ≥ 10 above baseline), notify nurse who in turn will discuss with physician.

Nortriptyline algorithm

1. Day 0: Start nortriptyline 25 mg qd.
2. Week 1: Call patient; assess side effects and adherence. Follow blood pressure protocol (with reminders if needed) similar to that used for venlafaxine.
3. Week 4: Assess PHQ-9, side effects; if inadequate response, increase to 50 mg qd.
4. Week 8: Assess PHQ-9, side effects; if inadequate response, consider nortriptyline blood level, as well as increase in dose to 75 mg qd.
5. Week 12: Assess PHQ-9, side effects; if inadequate response, consider alternative antidepressant.
6. Month 6: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
7. Month 9: Assess PHQ-9. If relapse, consider adjusting or changing antidepressants
8. Weaning off nortriptyline. If a medication change is needed do not stop nortriptyline abruptly. Decrease to half the patient's usual dose every 3 days until total daily dose is 25 mg, then discontinue. You may start the new antidepressant while weaning the nortriptyline.

ALGORITHM 4. COMBINATIONS

1. When to combine: When patient has had partial response to a given antidepressant, and is tolerating it well.
2. Common combinations
    a. Bupropion: added to SSRI (or possibly SNRI)
    b. Mirtazapine: added to SSRI or SNRI
    c. Nortriptyline: added to SSRI.

REFERRALS TO MENTAL HEALTH

Indicators for Mental Health Referral

1. Risk of harm to self (suicidal) or others (homicidal) will trigger urgent referral to primary care psychologist or suicide prevention coordinator.
2. Psychiatric comorbidity (e.g., substance use disorder; complex anxiety disorder; etc.)
3. Patient has many psychosocial issues that may benefit from psychotherapy or counseling
4. Patient desires psychotherapy or counseling instead of (or in addition) to antidepressants.
5. Patient requests or desires referral.
6. Poor responder (see below) to several steps of medication algorithm.

Poor responder

1. Mental health referral if all of the following 3 poor responder criteria are met:
    a. PHQ-9 or GAD-7 change from baseline < 5 on 2 consecutive calls
    b. Global depression or anxiety improvement < 4 ("somewhat better")
    c. Failed adequate trials of 2-3 different antidepressants, singly or in combination

Study Close-Out

1. Verify that the patient has an adequate amount of medication until he/she is able to follow-up with primary care physician (PCP).
2. Provide treatment synopsis to primary care physician (with copy to patient), summarizing type and dose of medications that patient is on.

Pharmacotherapy for Anxiety

At all stages of anxiety treatment, it is important to discuss a mental health referral, since specific types of psychotherapy (cognitive-behavioral therapy for some types of anxiety disorders or exposure therapy for other types) may be particularly helpful.

Step 1. SSRI or SNRI Antidepressant *

Priority	**Drug**	**Class**	**Efficacy †**	**Dose (in mg)**	
				Initial	**Increases**
1	Sertraline	SSRI	Panic, GAD, SAD, PTSD	50	100, 150
1	Paroxetine	SSRI	Panic, GAD, SAD, PTSD	20	30, 40
2	Venlafaxine	SNRI	Panic, GAD, SAD, PTSD	75	150, 225
2	Escitalopram		Panic, GAD, SAD	5	10,20
3	Fluoxetine	SSRI	Panic, PTSD	20	30, 40
3	Citalopram	SSRI	Panic	20	30,40
3	Duloxetine	SNRI	GAD	30	60

* For dosing details, see Antidepressant Guidelines on previous pages.

† Panic = panic disorder; GAD = generalized anxiety disorder; SAD = social anxiety disorder; PTSD = posttraumatic stress disorder

Step 2. Benzodiazepines *[only if primary care provider and/or mental health concurs]*

Priority	**Drug**	**Comments †**	**Daily Dose**	**Freq-uency**
1	Clonazepam	Long half-life reduces withdrawal symptoms from missed doses. Also, less risk of abuse.	1-4 mg	QD-BID
2	Lorazepam		4-12 mg	BID-TID
3	Alprazolam	More risk of withdrawal and abuse.	2-6 mg	TID-QID

- Evidence of anxiolytic efficacy for benzodiazepines (BZD) is less than for antidepressants
- What evidence exists is mainly for panic disorder and social anxiety disorder
- If BZD are used, short-term use (≤ 12 weeks) is preferred, while starting an antidepressant
- If used episodically, < 4 days per week use may be associated with less dependence

Step 3 (options)

- Combine an SSRI or SNRI antidepressant with a benzodiazepine
- Combine an SSRI with a tricyclic antidepressant (imipramine or nortriptyline)
- Consider buspirone 15-60 mg qd (BID-TID dosing) – equivocal evidence in GAD

APPENDIX 3

Operating Principles to Guide Clinical Decisions Regarding Treatment Changes for Pain		
	Principle	**Operational application (including examples)**
1	Concordance of criteria	Confidence in continuing the same treatment, or in making changes, is increased when clinical response criteria are concordant (i.e., all or most of the criteria show either a poor response or a good response)
2	Consistency of ratings	Ratings of chronic pain have an intrinsic variability (greater in some patients than in others), similar to variability in other chronic psychological (depression) and medical (hypertension, diabetes) conditions. Thus, treatment changes are best made when a consistent pattern (e.g., repeatedly high pain over several weeks) is documented.
3	Patient preferences	A "yes" response to criterion 4 (i.e., treatment change desired) will usually be honored, particularly if it is concordant with poor response on other criteria, and a safe, effective treatment option is available
4	Adverse effects	Honoring patient preferences must be balanced against potential adverse effects (e.g., medication side effects, drug-drug interactions, premature or excessive opioid use, high treatment costs, etc.)
5	Negotiated changes	The pros and cons of treatment changes are ideally negotiated by communication between the clinical team and an informed patient. In particular, when clinical response criteria are discordant (e.g., the patient desires a treatment change despite low pain interference ratings and/or global improvement, or the patient does not desire a treatment change despite persistently high pain interference and lack of global improvement), reasons for discordance should be probed.
6	Gradual improvement	Optimizing outcomes in a chronic condition like pain is often an incremental rather than immediate process, particularly when sequential treatment adjustments and behavioral interventions are required.
7	Benchmarks	A *partial* response in at least 2 of the first 3 clinical response criteria is the treatment goal by week 4, and a *target* response in at least 2 of 3 criteria is the goal by week 12.

APPENDIX 4

SUICIDAL IDEATION ALGORITHM

S1. Over the past 2 weeks, have you had thoughts of hurting or harming yourself?

0 NO → Done with this section → Go back to remainder of interview
1 YES [Continue with S2 below]
99 DON'T KNOW OR REFUSED TO ANSWER [Continue with S2 below]

S2. Have you thought about how you might actually hurt yourself?

0 NO
1 YES → [How? _____]
99 DON'T KNOW OR REFUSED TO ANSWER

S3. There's a big difference between having a thought and acting on a thought. How likely do you think it is that you will act on these thoughts about hurting yourself or ending your life sometime over the next month?"

0 Not at all likely
1 Somewhat likely
2 Very likely
99 DON'T KNOW OR REFUSED TO ANSWER

S4. Is there anything that would prevent or keep you from harming yourself?

0 NO
1 YES → [What? _____]
99 DON'T KNOW OR REFUSED TO ANSWER

S5. INTERVIEWER: IS THERE ANY SHADED RESPONSE TO ITEMS S2, S3 OR S4?

0 NO → 1) Complete interview
1 YES → 1) Complete interview
2) Follow steps on next page

Action Today

➔ For patients with **YES on S5** (i.e., a shaded response on prior page to S2, S3, or S4)

1) **Before getting off the phone with the subject:**
   a. Ask if he/she has been seen in mental health (psychiatry, psychology, etc.)
      i. Currently (if so, do they have an appointment sometime soon?)
      ii. In the past but not currently
      iii. Never
   b. Note that you would like to review the information with study doctor, and that you will call the patient back within the next hour. Verify the phone number he/she will be at for the next hour.

2) **Discuss with physician** by phone, making calls in following order:

Order	Physician	Cell	Pager	Office
1	Kurt Kroenke	474-5753	none	630-7447
2	Matt Bair	287-9469	310-4058	988-2058
3	Other HSR&D MD	*not applicable*	*not applicable*	VA HSR&D
4	VA Suicide Resources → see next page			

3) **Notify Project Coordinator (Erica Evans)** who will
   a. Check to see if patient is a CSM intervention group patient. If so, she will inform study nurse, Sharon Weitlauf.
   b. File a copy of this form in the subject's study file and document the AE and follow-up in the the AE spreadsheet.
   c. Note this as either an:
      i. AE (if no same-day mental health referral)
      ii. SAE (if same day mental health referral)

***** *See next page for more urgent VA suicide prevention resources* *****

Roudebush VAMC Suicide Prevention Resources

1. On-site → participant is present in our Roudebush VAMC
    a. Suicide prevention coordinators

Name	Role	Office phone	Pager
Travis Field	Suicide coordinator	988-3213	310-4202
Judi Green	Case manager	988-3365	310-4025
Christina McNeely	Case manager	988-4327	310-4177

    b. The current protocol at the VA is to escort the patient to the emergency room.

2. On phone →
    a. Ask where patient currently is (what address).
    b. Do warm phone transfer to Suicide Hotline if situation appears urgent (i.e., patient is contemplating suicide today).

To Conference:

- *Do not* put the caller on hold
- Push **Transfer**
- **Dial** the extension or outside phone number
    - This puts the caller on hold and they will hear hold music while you are able to speak to the person you are eventually transferring to
- Push **Conference**
    - All three parties will be able to speak to each other
- When ready to let the other two parties speak privately, **hang up**
- *Do not* push transfer or conference again
- **If patient hangs up and does not answer when you call back, call 911.**

Phone number for **Veteran Crisis Line** is 1-800-273-TALK (8255)