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

Study Design and Sample Characteristics

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Key words: pain, depression, anxiety, telemedicine, clinical trial

Abstract

Background**.** Pain is the most common presenting somatic symptom in medical outpatients, and depression and anxiety are the two most common mental disorders. They frequently co-occur, are under-treated, and result in substantial disability and reduced health-related quality of life.

Objectives. The *Comprehensive vs. Assisted Management of Mood and Pain Symptoms (CAMMPS)* study is a randomized comparative effectiveness trial designed to test the relative effectiveness of a lower-resource vs. a higher-resource technology-assisted intervention for the management of patients suffering from pain plus anxiety and/or depression.

Methods/Design. CAMMPS has enrolled 294 primary care patients with chronic pain plus comorbid anxiety and/or depression and randomized them to either: 1) *Assisted Symptom Management* (ASM) consisting of automated symptom monitoring by interactive voice recording or Internet and prompted pain and mood self-management; or 2) *Comprehensive Symptom Management* (CSM) which combines ASM with optimized medication management delivered by a nurse-physician specialist team and facilitated mental health care. Outcomes are assessed at baseline, 1, 3, 6, and 12 months. The primary outcome is a composite pain-anxiety-depression (PAD) severity score. Secondary outcomes include individual pain, anxiety, and depression scores, health-related quality of life, disability, healthcare utilization, and treatment satisfaction.

Discussion. CAMMPS provides an integrated approach to PAD symptoms rather than fragmented care of single symptoms; coordinated symptom management in partnership with primary care clinicians and psychologists embedded in primary care; efficient use of health information technology; attention to physical and psychological symptom comorbidity; and the coupling of self-management with optimized medication management and facilitated mental health care.

Keywords**:** patient-reported outcome, pain, depression, telehealth, clinical trial

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1. Introduction

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]. Indeed, persistent pain is a major international health problem, prompting the World Health Organization to endorse a global campaign against pain [4].

Musculoskeletal pain is consistently the most common, disabling, and costly of all pain complaints [5]. 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 Veteran Administration (VA) clinics, more than 80% of all pain complaints expressed by Veterans were musculoskeletal in nature [6]. 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].

Depression and anxiety are the two most common mental health problems seen in the general medical setting, each being present in 10%-15% of primary care patients [8-10]. 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]. Additionally, depression and anxiety each result in substantial health care costs as well as indirect costs due to lost work productivity [13, 14].

Pain, anxiety, and depression are often inextricably linked (i.e., the *PAD triad*), such that disentanglement is scientifically and clinically impractical [15-17]. Moreover, PAD symptoms have reciprocal negative effects on treatment response of one another, and additive adverse effects on health outcomes [18-20]. Thus, interventions that target the PAD

symptoms collectively rather than individually are desirable. Also, since most patients with PAD symptoms are treated predominantly or exclusively in primary care, PAD interventions that are collaborative with or integrated into primary care are likely to have the greatest impact [10].

Comprehensive vs. Assisted Management of Mood and Pain Symptoms (CAMMPS) is a randomized comparative effectiveness trial comparing two pragmatic interventions (an intensive vs. a low-resource approach) for treating the pain plus anxiety and/or depression. The assisted symptom management arm (ASM) intervention consists of automated symptom monitoring and prompted pain and mood self-management. The comprehensive symptom management (CSM) intervention combines ASM with optimized medication management and facilitated mental health care by a centralized nurse-physician team. The primary aim is to compare the 12-month effectiveness of CSM vs. ASM in improving overall pain and mental health. Secondary outcomes will include health-related quality of life, disability, health care utilization, and treatment satisfaction.

2. Methods

2.1. Overview of Study Design and Research Aims and Hypotheses

CAMMPS is a 12-month randomized comparative effectiveness trial comparing a low-resource entirely automated intervention to a more intense comprehensive intervention that complements the automated intervention with a nurse-physician team collaborating with the primary care team through a largely telecare approach (i.e., most communication with patients and providers is by telephone or through secure e-mails and websites). Outcomes are assessed at 1, 3, 6, and 12 months. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). CAMMPS has been reviewed and approved by the Indiana University Institutional Review Board and the VA Research Review Committee.

CAMMPS has one primary aim, two secondary aims, and one exploratory 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 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 individual pain, anxiety, and depression scores.

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

Aim 4. To explore patient-perceived barriers and facilitators of the CAMMPS intervention and the relative contribution of each intervention component to overall symptom improvement.

2.2. Conceptual Model

Figure 1 depicts the conceptual model underlying the CAMMPS trial. The 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 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 may lead to an improvement in the primary (proximal) outcome, namely symptom burden as measured by the composite PAD symptom 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 utilization.

2.3. Eligibility

The study population consists of Veterans 18 years and older receiving care from one of 5 primary care clinics at a large VA Medical Center in the Midwest. Patients are eligible if they have pain plus psychiatric comorbidity.

Pain must meet all of the 3 following criteria: (1) musculoskeletal, either localized (in the arms, legs, back, or neck) or widespread (fibromyalgia); (2) persistent for 3 months or longer [21, 22] despite a trial of at least one analgesic medication; (3) at least moderate in severity, defined as a Brief Pain Inventory average severity score of 5 or greater in the past

week [23] or having at least moderately interfered with work or other activities in the past month.

Psychiatric comorbidity must meet any 1 of the following 3 criteria.

(1) *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. 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 [24, 25].

(2) *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 [26, 27]. 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.

(3) *Mixed anxiety-depression* is defined as combined PHQ-8 and GAD-7 score ≥ 12. Scores of 6 or higher on each scale represent at least mild depression or anxiety symptoms, respectively [26], and this level of symptoms has been shown responsive to treatment [28].

Excluded are individuals who: (a) do not speak English; (b) have moderately severe cognitive impairment as defined by a validated 6-item cognitive screener [29]; (c) have schizophrenia, bipolar disorder or other psychosis; (d) have a severe or complex mental illness or exhibit suicidal thoughts as their condition is unsuitable for a predominantly telecare intervention; (e) are pregnant; (f) have an anticipated life expectancy of less than 12 months.

2.4. Recruitment and Randomization

Physicians working in the 5 primary care clinics were informed of the study in detail and were asked for permission to contact their patients for possible participation in the study. Since this trial is a collaborative care intervention, only patients whose physicians provided

consent were enrolled. Electronic medical records are used to create a master list of individuals who, within the preceding 36 months, have received an ICD diagnosis of musculoskeletal pain condition and either a depressive or anxiety disorder. This patient list was updated quarterly during the enrollment period. A letter briefly describing CAMMPS that included a 2-item pain severity and interference scale was mailed to patients on this list who could either contact the study coordinator or return a form indicating their interest in the study eligibility interview. Individuals indicating interest and screening positive for moderate pain severity or interference were contacted by phone and assessed for study eligibility. Eligible patients who were interested in participating were scheduled for an initial study visit where, after providing written informed consent, underwent a baseline study interview conducted by a research assistant.

Participants then met with a project coordinator who performed the randomization to keep the two research assistants responsible for outcome assessments blinded to treatment arm assignment. Allocation to treatment arm was carried out by a computer-generated randomization list with randomly varying block sizes of 4 and 8 to maximize allocation concealment. Study participants are reimbursed $25 for each of the study interviews completed (baseline and 4 follow-up interviews) and continue to receive all their standard VA medical care.

2.5. Data Collection Protocol

Table 1 outlines the data collection protocol, including the variables that are measured, number of items, internal reliability (Cronbach's coefficient alpha) for scales, and time points for assessment. All assessments are conducted by a research assistant blinded to study group.

2.5.1. Primary outcome measure

The primary outcome measure is 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, 7 for anxiety, and 9 for depression. Each of these measures has proven sensitive to change in treatment trials [30-32]. 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.

As an important secondary outcome, a composite pain-anxiety-depression score from the PROMIS measures (www.healthmeasures.net) will be calculated, using the 8 item scales for depression and anxiety and pain from the PROMIS-57 Profile [33]. 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 with PROMIS pain, anxiety and depression scores of 66, 58, and 53 would have a composite score of 59.

2.5.2. Other measures

Clinical response is assessed for pain and mood using a 7-item patient-rated global change scale (much better, moderately better, a little better, same, a little worse, moderately worse, much worse) [34]. Three secondary anxiety measures include the PTSD Checklist (PCL) to assess the presence and severity of posttraumatic disorder [35]; the Hopkins Symptom Checklist 10-item anxiety scale [36]; and the Mini-SPIN 3-item screener for social anxiety disorder [37]. Two measures of somatization include the Patient Health Questionnaire 15-item somatic symptom scale (excluding the sexual problem item) [26] and the 8-item Somatic Symptom Scale [38]. Health-related quality of life is assessed with the Medical Outcomes Study Short-Form 12-item scale from which a Physical Component Summary score and Mental Component Summary score can be derived [39]; additionally, 8 items from the SF-36 were included which, along with items from the SF-12, provide the full SF-36 social functioning, bodily pain, vitality and mental health scales [40]. Patient-rated disability is assessed with the 3-item Sheehan Disability Scale [41] and 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 percent effectiveness at work [23]. Additional scales include the 6-item pain catastrophizing scale from the Coping Strategies Questionnaire [42]; the 5-item REMIT scale which has shown to be useful in predicting depression remission [43]; and the PROMIS 4-item scales for fatigue and sleep problems [44], two symptoms that frequently co-occur with pain, anxiety and depression.

Medical comorbidity is assessed with a validated 9-disease checklist [45]. Substance use is assessed with the AUDIT-C for alcohol [46] as well as questions about the use of tobacco, illicit drugs, and family history [23]. Health care utilization (outpatient visits, emergency department visits, and hospitalizations) and treatments (medications and nonpharmacological treatments specific to pain and mental health) are assessed using an interview coupled with electronic medical review (EMR). Satisfaction with pain and mood treatments as well as the automated and nurse care manager components of the interventions are assessed with items used in previous trials [23, 25]. Three diagnostic variables were created: probable major depressive disorder using the PHQ-9 diagnostic algorithm [26]; probable PTSD using a PTSD Checklist (PCL) score ≥ 41 [47]; and substance use risk derived from 13 items and categorized as low, intermediate, and high risk [23].

2.6. Assisted Symptom Management (ASM) Intervention

ASM has 2 principal components: automated symptom monitoring and prompted pain and mood self-management. Study participants complete regular symptom surveys either by interactive voice recorded (IVR) telephone calls or Internet (based upon patient preference); both IVR and internet approaches use push-technology (automated calls or e-mail reminders) to optimize patient outreach. The schedule is 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 to the acute phase of initial treatment and dose adjustment or adding/switching medications, followed by less frequent monitoring during the relapse prevention phase. Since all patients have threshold levels of pain as well as depression and/or anxiety, more up-front intensive monitoring with initiation and adjustment

of symptom therapy followed by a tapering schedule is both rational and evidence-based [28, 48]. The core survey includes 15 items: a) brief pain (PEG), anxiety (GAD-2) and depression (PHQ-2) measures [26, 30]; b) items on sleep, fatigue, and irritability; c) items about global change (better, same, worse), and the degree to which symptoms have interfered with daily activities; and d) 3 items to prompt use of the pain and mood self-management units.

The Pain and Mood Self-Management Program includes approximately 12 hours of web-based instruction divided into 9 units (coping with pain; pain medications; communicating with providers; depression; anxiety; sleep; anger management; cognitive strategies; and problem-solving). For participants without Internet access, binders with the program materials were provided. These topics are partly derived from the nurse-administered self-management program in previous trials [49, 50] and link to several public domain VA and non-VA websites with interactive self-management programs. Subjects are instructed in how to use the program by the nurse (CSM group) or project coordinator (ASM group). The web-based delivery of the program coupled with automated reminders to proceed through the 9 units is intended to enhance completion of the program.

2.7. Comprehensive Symptom Management (CSM) Intervention

2.7.1. CSM Structure and Overview

This arm couples telecare management by a nurse-physician team with ASM, thus testing "combined" therapy vs. "monotherapy" (ASM only). As illustrated in our conceptual model (Figure 1), 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 education, motivation, and coordination of care through periodic telephone contacts. 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 a "treat to target" approach [10].

The nurse has *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. The nurse monitors trend reports weekly, responds to automated monitoring clinical alerts and patient calls daily, and serves as the coordinating linchpin between patient, supervising physician symptom specialist, primary care physician, and psychologist or other mental health specialist. The nurse has 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 to discuss enrolled patients not responding to therapy.

2.7.2. Augmented Automated Symptom Monitoring for the CSM Arm

All patients randomized to the CSM arm receive the core ASM as described in section 2.6 above. However, ASM is enhanced in four ways for patients in the CSM arm to take advantage of the "technology-human" partnership provided by the centralized nurse care manager-physician team. First, the 15-item core ASM survey is augmented by 5 additional items: medication adherence, side effects, desire for treatment changes, and request for a nurse care manager call. Second, patients can leave a recorded message for the nurse who in turn can leave recorded messages for patients. Third, ASM responses are tabulated in a trend report on a secure website. Trend reports are reviewed weekly by the nurse care manager. Fourth, e-mail alerts are sent to the nurse to trigger patient calls for medication side effects, patient requests for treatment change or a nurse call, or missed ASM reports.

2.7.3. Facilitated Mental Health Care

Figure 2 summarizes the options for facilitated mental health care. Patients are offered an option of psychotropic medications, referral to a psychologist embedded in primary care for psychotherapeutic treatment, or combined therapy. Those who prefer medication are offered a referral to psychiatry, but those who refuse referral have the option of a psychotropic prescription from their primary care physician. Those with PTSD are especially encouraged to accept a mental health referral. Moreover, patients not responding to one treatment are encouraged to consider combined therapy and/or mental health referral. 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 are provided to the

treating psychologist as one metric of treatment response to determine if additional treatment sessions or modifications to treatment may be warranted.

2.7.4 Optimized Pharmacotherapy

The nurse care manager obtains a detailed history of current and past analgesic and psychotropic use as well as patient-recalled effectiveness and tolerability. Based upon this, the nurse-physician team develops an initial treatment plan based upon evidence-based medication algorithms used in previous trials [28, 48, 51]. The stepped care analgesic algorithm includes: 1) acetaminophen or a nonsteroidal anti-inflammatory drug; 2) tricyclic antidepressants (amitriptyline, nortriptyline); 3) muscle relaxants (cyclobenzaprine, methacarbamol, tizanidine), gabapentinoids (gabapentin, pregabalin), or serotonin-norepinephrine reuptake inhibitors [SNRI] (duloxetine, venlafaxine). Topical analgesics (diclofenac cream, capsaicin, lidocaine) can be considered for areas of localized pain. Controlled analgesics (tramadol or opioids) are not discontinued for patients taking them on study enrollment but are not part of the analgesic algorithm for this trial.

Psychotropic medication is prescribed either by a mental health specialist or the primary care physician depending upon patient preferences (Figure 2). Due to their efficacy for both depression and anxiety, antidepressants are typically the preferred initial medication. These typically are either a selective serotonin reuptake inhibitor (SSRI), an SNRI, bupropion, or mirtazapine. Patients referred to psychiatry for more complex disorders (including PTSD) might receive a broader array of psychotropics based upon type of disorder and treatment response.

2.7.5. Duration of Intervention

This 12-month study is divided into 2 phases: (1) *acute* phase (first 6 months) during which automated symptom monitoring occurs weekly for the first month and then every other week during 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 occurs once a month to allow further treatment adjustments in subjects who fail to achieve target clinical responses during the acute phase or to detect relapse in subjects who

do achieve target responses. Automated symptom monitoring allows nurse care manager contacts to be selective, thereby making 12-month surveillance more efficient.[52]

2.7.6. Determining Treatment Changes

The algorithm for determining treatment changes (**Figure 3**) is based upon 3 criteria: 1) symptom severity of pain, anxiety and depression as assessed by the PEG, GAD-2, and PHQ-2 scores recorded in the ASM reports; 2) global rating of change which, if the patient reports improvement, is further categorized as a little better, moderately better, or a lot better; 3) patient response to the question – "Would you like to make some changes in the treatment for your pain [mood]". These 3 criteria assess the core outcome domains recommended by IMMPACT: symptom intensity/interference, patient-rated global improvement, and satisfaction with treatment [34, 53]. A ≥ 30% reduction 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, anxiety, and depression 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 are regularly assessed and applied by the nurse-MD symptom team in their weekly case management meetings. Clinical decision making is guided by the algorithm in Figure 3.

2.8. Statistical considerations

2.8.1. Sample size determination.

Sample size is determined to ensure adequate power for our primary hypothesis that CSM is superior to ASM in reducing composite PAD symptom severity. In our previous 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 [48, 49]. Since CAMMPS is comparing CSM to an active comparator ASM group rather than a usual care control group, we estimate a smaller effect size of 0.35, which is half way between a small (0.2) and moderate (0.5) effect size [54]. The 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 as the scale score minus the sample mean divided by the sample standard deviation [55]. 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 provides 80% power to detect a between-group effect size difference of 0.35 using a two-sample t-test with a 5% Type I error rate. Allowing for 15% attrition in our present trial, we initially projected a need for 150 per treatment arm, or a total of 300 participants. Two-thirds of the way through enrollment, the attrition was less than 10%, indicating that a sample size of 286 would be sufficient.

2.8.2. Statistical analyses

All analyses will be based on intention-to-treat in all randomized participants. 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 over the 12-month period of the trial using mixed effects model repeated measures (MMRM) analysis [48, 49]. 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. A random intercept will be used to adjust for within-subject correlation. Time-specific (1, 3, 6, and 12 months) between-group differences will also be compared.

Similarly, MMRM will be used to compare groups on: 1) two secondary measures of overall improvement including the composite PROMIS pain-anxiety-depression score, and

patient-reported global improvement of pain and mood; 2) individual pain, anxiety, and depression scores (Aim 2); and 3) health-related quality of life, disability, and treatment satisfaction (Aim 3). To accommodate the large variability of health care utilization data, negative binomial distribution regression analysis will be used to model count data. For all secondary outcomes, the p-values will be adjusted for multiplicity using the Sidak method [56] where: adjusted p-value = $1 - (1 - \text{unadjusted p-value})^{\#\text{tests}}$ Analyses will be performed using SAS Version 9.3.

Aim 4 will explore the independent effects of each of the 5 intervention components highlighted in the conceptual model (Figure 1). Analyses for this aim will include only CSM participants since they received all 5 active components. The 5 components will be quantified as follows: 1) automated monitoring contacts (total number); 2) self-management modules completed (range, 0 to 9); 3) medication changes (new analgesic and psychotropic starts and changes during the 12-month trial); 4) nurse contacts (total number); 5) mental health visits (total number). Linear regression models will be run for each of the 5 components (in separate models and together) with the 12-month change in PAD composite score as the dependent variable and the specific components as predictor variables.

2.9. Qualitative interviews and analysis

A subsample of individuals completing their 12-month participation in the trial will be asked if they are interested in being interviewed about their experience with the CAMMPS intervention, and those willing to participate will complete written informed consent. Purposeful sampling will be used to include participants from both CSM and ASM arms as well as those who were improved vs. same or worse on patient-reported global rating of change. As with previous studies, we expect thematic saturation to occur after interviewing 20 to 25 study participants [57,58]. An interview guide combining open-ended questions with a series of probing questions will be used to elicit perceived barriers and facilitators to key components of the interventions. Audio recordings of the 30 to 60 minute interviews will be transcribed, de-identified, and checked for accuracy. A team of analysts will use an immersion-crystallization approach to analyze the qualitative data. Discrepancies will be

resolved by consensus [59].

3. Results

Figure 4 shows the results of screening, eligibility determination, and enrollment, which was conducted from January 2014 through June 2016. Letters were mailed to 5596 patients with an appropriate musculoskeletal pain or mental disorder ICD code of whom 1549 expressed potential interest in the study by returning a letter or calling a study phone number. Of the 1176 patients who completed an eligibility interview, 397 met study eligibility criteria. The most common reasons for not being eligible were pain or depression/anxiety scores that were too low, or mental health problems that were too complex for a telecare intervention. Of the 397 eligible patients, 294 (74%) enrolled in the study and were randomized to the CSM (n = 147) or ASM (n = 147) arms of the trial.

Randomization resulted in comparable groups on all measured variables (**Table 2)** except one: probable PTSD was slightly more prevalent in the ASM arm although severity scores as measured by the PTSD checklist were similar between groups. Overall, the sample had a mean age of 57.4 years (range, 25 to 88); 87.4% were men; 79.3% were white, 15.3% black, and 5.4% other race; 56.8% married; 27.9% were employed, 38.1% currently unemployed, and 34.0% retired; 21.1% were college graduates, 53.1% had some college or trade school, and 25.9% had only a high school diploma or GED. Income level was reported as "comfortable" by 39.2% of patients, "just enough to make ends meet" by 41.2%, and "not enough to make ends meet" by 19.6%. Diagnostic thresholds for probable major depressive disorder and probable PTSD were met by 162 (55.1%) and 163 (55.4%) of study participants, respectively. In terms of risk for substance use risk, 11.9% of patients were classified as high risk, 39.1% as intermediate risk, and 49.0% as low risk.

The mean baseline BPI total pain score was 5.9, with a mean BPI interference score of 6.1 and mean BPI severity score of 5.5, representing a moderate level of pain. The duration of pain was 3 to 12 months in 2.7% (n=8) of the patients, 1 to 5 years in 20.7% (n=61), 6 to 10 years in 19.4% (n=57), and more than 10 years in 57.1% (n=168). The median number of painful bodily sites (from a checklist of 17 sites) was 5. Only 4.4% (n=13)

of the patients reported a single site of pain, whereas 2 sites were reported by 11.2% (n=33), 3 sites by 17.7% (n=52), 4 sites by 15.0% (n=44), 5 sites by 13.6% (n=40), 6 sites by 12.9% (n=38), 7 sites by 9.2% (n=27), 8 to 9 sites by 11.2% (n=33), and ≥ 10 sites by 4.8% (n=14).

There were no significant differences between the intervention and usual care groups in terms of duration of pain or the number of pain sites. Patients reported that they had to cut down on their usual activities for one-half day or more on 15.4 days in the past 4 weeks, and work effectiveness was only 61%. Multiple domains of health-related quality of life were also substantially diminished.

4. Discussion

CAMMPS successfully enrolled 294 primary care patients with chronic musculoskeletal pain and comorbid depression/anxiety, slightly exceeding the enrollment goal of 286 participants. Nearly three-fourths of eligible patients consented to participate, and randomization produced comparable intervention and control groups. The sample had moderately severe levels of pain as well as depression and anxiety, and major depression and posttraumatic stress disorder were each present in more than half of study participants. Self-reported disability was substantial, and there were major decrements in health-related quality of life.

CAMMPS focuses 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 sub-optimally 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.

One limitation of CAMMPS is the exclusively Veteran sample that was predominantly white men who had a moderate degree of unemployment and financial constraints. Moreover, the focus on patients with both chronic pain and psychiatric comorbidity resulted in relatively high rates of self-reported disability and functional impairment. However, if CAMMPS proves effective, the results may provide a conservative estimate of benefits given the complex nature of both the patients' disorders as well as life circumstances. A second limitation is the potential for selection bias arising from unmeasured differences between patients not responding to our mailed invitation and those we were able to contact by phone (Figure 4). On the other hand, enrollment rates were high among those we were able to contact and who met study eligibility criteria. Third, the multicomponent nature of the CAMMPS intervention means that the specific effects of individual components will be difficult to unbundle from the overall effects of the intervention. However, this is true for many complex interventions for chronic disease [10, 60], and our proposed exploratory analyses may at least partly isolate the relative contributions of specific components.

In summary, 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 clinician-administered pharmacological and behavioral 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 telecare services as well as patient-aligned care teams (PACTs) in

the VA or, in non-VA settings, patient-centered medical homes and accountable care organizations.

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Conflicts of Interest

None of the authors have any conflicts of interest to disclose.

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Table 1. CAMMPS Outcome Assessment: Measures and Schedule of Administration

Domain	Measure	# Items	Alpha	Schedule (Month)				
				0	1	3	6	12
Primary PAD composite								
• Pain	• Brief Pain Inventory	11	0.89	X	X	X	X	X
• Anxiety	• GAD-7 anxiety	7	0.79	X	X	X	X	X
• Depression	• PHQ-9 depression	9	0.73	X	X	X	X	X
Secondary PAD composite								
• Pain	• PROMIS pain	8	0.91	X		X	X	X
• Anxiety	• PROMIS anxiety	8	0.91	X		X	X	X
• Depression	• PROMIS depression	8	0.93	X		X	X	X
Clinical response	Global Rating of Change	2	n/a		X	X	X	X
Anxiety – secondary scales	PTSD Checklist	17	0.91	X		X		X
	Mini-SPIN social anxiety	3	0.84	X				
	HSCL anxiety	10	0.90	X		X		X
Somatization	PHQ-somatic	14	0.66	X				X
	SSS-8	8	0.72	X				X
Health-related quality of life (Medical Outcomes Study Short-Form [SF] scales)	SF-12 + 8 other SF items	20						
	• Physical Component	--	0.85	X		X		X
	• Mental Component	--	0.85	X		X		X
	• SF-36 Social Functioning	--	0.86	X		X		X
	• SF-36 Bodily Pain	--	0.72	X		X		X
	• SF-36 Vitality	--	0.75	X		X		X
	• SF-36 Mental Health	--	0.79	X		X		X
Disability	Sheehan Disability Scale	3	0.85	X		X	X	X
	Disability days past 4 wks	2	n/a	X		X	X	X
Pain catastrophizing	CSQ catastrophizing	6	0.87	X			X	X
Depression remission tool	REMIT scale	5	0.76	X		X	X	X
Fatigue	PROMIS fatigue	4	0.90	X		X		X
Sleep	PROMIS sleep	4	0.77	X		X		X
Sociodemographics	age, race, sex, education, marital, job status, income	7	n/a	X				
Medical comorbidity	Checklist of 9 diseases	9	n/a	X				
Substance use	alcohol, tobacco, illicit drugs	13	n/a	X				
Health care use	Electronic medical records	5	n/a					X
Treatment for PAD	PAD-specific treatments	15	n/a	X			X	X
Treatment satisfaction	PAD-specific satisfaction	4	n/a			X		X
Intervention satisfaction	Automated monitoring and care management	9	n/a					X

Table 2. Baseline Characteristics of 294 Subjects Enrolled in the CAMMPS Study

Characteristic	**CSM Group** (n = 147)	**ASM Group** (n = 147)
Age in years, mean (SD)	56.9 (12.5)	57.9 (11.7)
Sex, % men	84.4	90.5
Race, % white	78.9	79.6
Education, % > high school	72.8	74.5
Married, %	58.5	55.1
Current smoker, %	27.2	24.5
Major depression (probable), %	55.8	54.4
Posttraumatic stress disorder (probable), %*	49.7	61.2
Substance use risk intermediate to high, %	55.1	46.9
Comorbid medical diseases, mean (SD)	2.3 (1.4)	2.3 (1.4)
Pain scale scores [range], mean (SD) †		
BPI pain total [0-**10**]	6.1 (2.0)	6.0 (1.9)
SF-36 pain [**0**-100]	29.3 (15.3)	29.8 (16.5)
PROMIS 8-item pain T-score [0-**100**; 50 = norm]	64.5 (5.5)	64.1 (5.9)
CSQ pain catastrophizing [0-**36**]	19.0 (8.8)	17.7 (9.2)
Psychological scale scores [range], mean (SD) †		
PHQ-9 depression [0-**27**]	14.4 (5.1)	13.7 (5.3)
GAD-7 anxiety [0-**21**]	11.3 (5.0)	11.1 (5.3)
PROMIS 8-item depression T-score [0-**100**; 50 = norm]	58.7 (8.0)	58.5 (8.7)
PROMIS 8-item anxiety T-score [0-**100**; 50 = norm]	61.2 (8.2)	60.8 (8.9)
SF-36 mental health [**0**-100]	51.9 (19.6)	52.7 (198)
Mini-SPIN social anxiety [0-**12**]	4.8 (3.9)	4.2 (3.7)
HSCL anxiety [0-**4**]	1.2 (0.8)	1.3 (1.0)
PTSD Checklist [17-**85**]	44.1 (14.7)	45.5 (15.4)
REMIT depression remission score [0-**20**]	9.1 (3.8)	8.9 (3.8)
PHQ-14 somatization [0-**28**]	13.9 (3.9)	13.2 (4.2)
SSS-8 somatization [0-**32**]	17.1 (5.6)	16.3 (6.0)
AUDIT-C alcohol use [0-**12**]	2.2 (2.0)	2.7 (2.7)
Health-related quality of life scores [range], mean (SD) †		
SF-12 physical component summary [norm = 50]	33.2 (8.6)	33.2 (8.4)
SF-12 mental component summary [norm = 50]	37.5 (11.2)	38.2 (10.1)
SF-36 general health perceptions [**0**-100]	37.9 (27.0)	37.8 (29.0)
SF-36 social functioning [**0**-100]	43.3 (26.1)	43.6 (26.6)
SF-36 vitality [**0**-100]	27.6 (17.0)	27.5 (20.4)
PROMIS 4-item fatigue T-score [0-**100;** 50 = norm]	63.6 (8.2)	62.9 (8.3)
PROMIS 4-item sleep T-score [0-**100;** 50 = norm]	59.6 (7.6)	59.7 (7.8)
Disability scores [range], mean (SD) †		
Sheehan Disability Index [0-**10**]	5.7 (2.3)	5.7 (2.4)
Health-related disability days past 4 weeks [0-**28**]	15.7 (9.1)	15.2 (9.7)
Percent work effectiveness [**0**-100]	60.1 (25.2)	61.6 (28.0)

* P = .047. There were no other significant differences between intervention and usual care groups

† For scale scores, the *range* is the minimum to maximum possible score on the scale, and the **bolded** number represents the worst score on the scale.

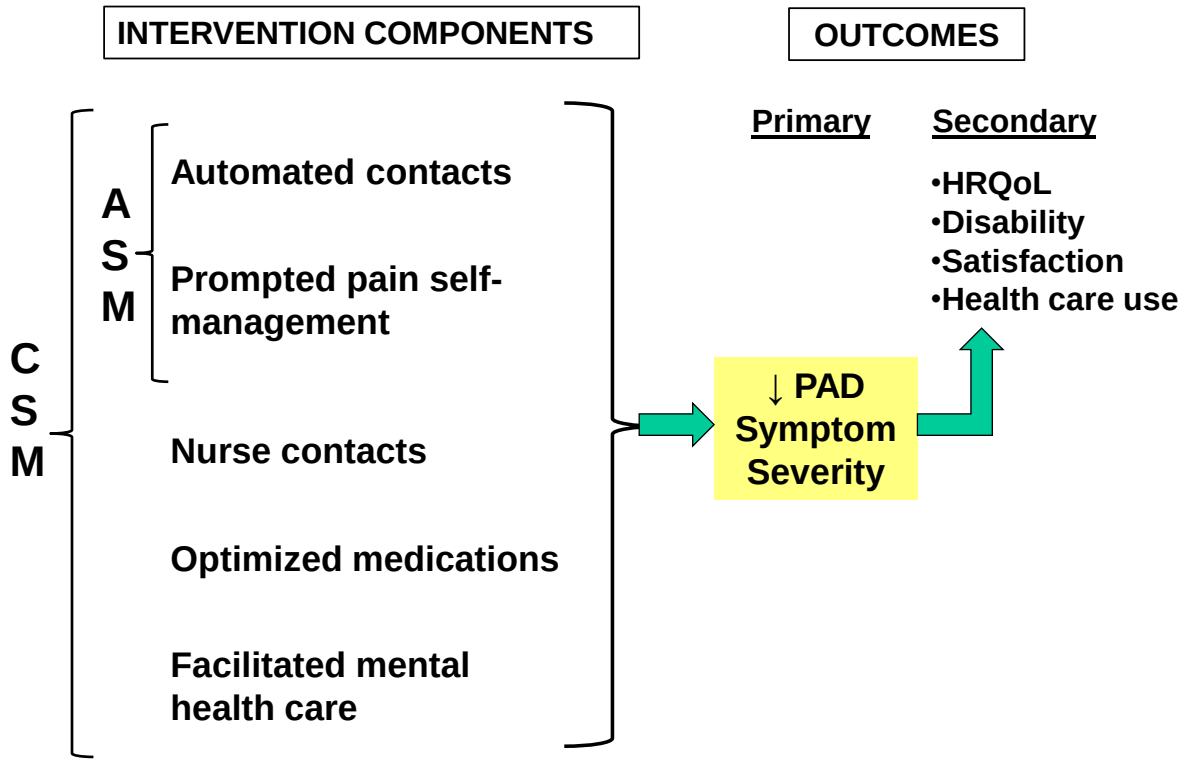
Legends

Figure 1. Conceptual model for CAMMPS trial, illustrating the 2 components of the automated symptom management (ASM) intervention and the 3 additional components of the comprehensive symptom management (CSM) intervention. Also, the primary outcome that the intervention is hypothesized to benefit is depicted as well as the secondary outcomes postulated to parallel improvements in the primary outcome.

Figure 2. Facilitated mental health care protocol for Comprehensive Symptom Management group.

Figure 3. Criteria-based algorithm for adjusting pain, anxiety and depression treatment.

Figure 4. Flow diagram of participant screening, eligibility and enrollment. A) Other reasons included living out of state (n=43), life expectancy less than 12 months (n=31), no VA primary care physician (n=29), deceased (n=23), cognitive impairment (n=20), severe visual or hearing impairment (n=12), pain less than 3 months (n=9), no analgesics tried (n=6), and other (n=8). B) Indeterminate eligibility in 245 individuals who refused to do an eligibility interview and 128 who could not be contacted.



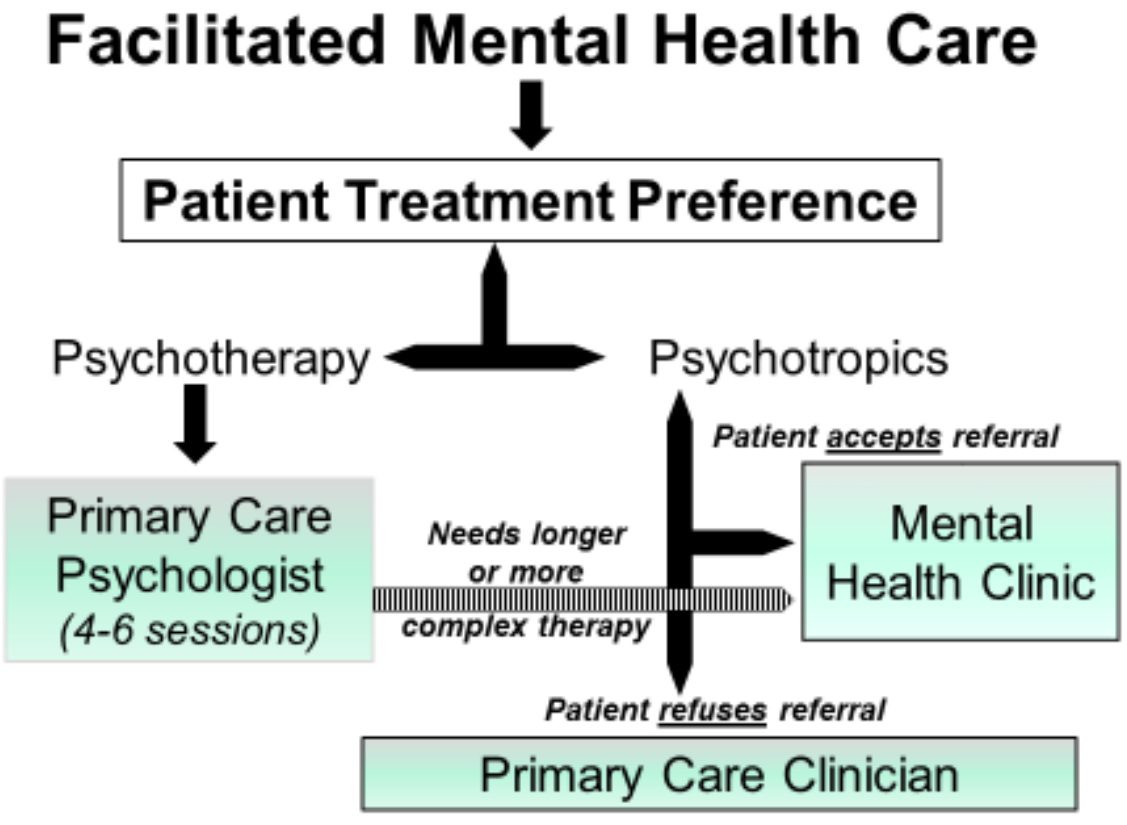


Figure 3. Algorithm for Using Clinical Criteria to Decide on Treatment Changes

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")