NCT01799213

Discontinuing NSAIDs in Veterans With Knee Osteoarthritis

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ABBREVIATIONS

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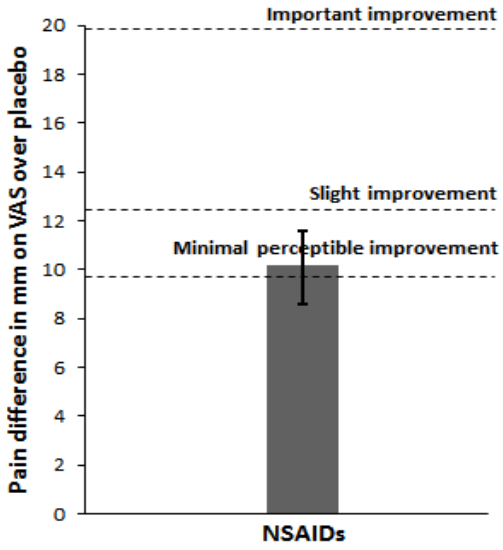
AEs: Adverse Events
AUC: Area Under the Curve
ASA: Aspirin
CBT: Cognitive Behavioral Therapy
COX-2: Cyclooxygenase-2
EMR: Electronic Medical Record
EBP: Evidence-Base Psychotherapy
HUI3: Health Utility Index Mark 3
ICER: Incremental Cost Effectiveness Ratio
ITT: Intent-to-Treat
LME: Linear Mixed Effects
MCID: Minimally Clinically Difference
NSAIDs: Nonsteroidal Anti-Inflammatory Drugs
OA: Osteoarthritis
OTC: Over-the-Counter
PP: Per Protocol
PPI: Proton Pump Inhibitor
PRIME: Pain Research Informatics Medical Comorbidity and Education
QALY: Quality Adjusted Life Year
RCT: Randomized Controlled Trial
RDW: Regional Data Warehouse
RWT: Randomized Withdrawal Trial
Rx: Prescription
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
VACHS: VA Connecticut Healthcare System

A. RESEARCH PLAN

A.1 Overview: Knee osteoarthritis (OA) is a major cause of disability among Veterans [1]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications for this disorder [2] with over 50% of people with OA reporting regular use [3]. While short-term studies have demonstrated that NSAIDs are more effective than placebo and acetaminophen, there are no long-term data supporting the use of these medications [2,4]. Maximum benefits are reported within 1 month and the single published long-term study showed no significant difference in knee pain at 1 year between NSAIDs and placebo [5]. Moreover, the decrease in pain conferred by NSAIDs does not meet patient-defined thresholds indicating clinically significant improvement (Figure 1) [6]. Given these data and the substantial morbidity associated with long-term NSAID use, discontinuation trials to determine whether there is a clinically significant incremental benefit of NSAIDs over and above placebo are warranted.

Figure 1. Effect of NSAIDs over Placebo



The objectives of this proposal are to determine whether 1) placebo is as effective as continued NSAIDs, and 2) cognitive behavioral therapy (CBT) is a viable alternative to continued NSAID use. While acetaminophen is also a viable alternative, the vast majority of patients with knee OA have failed this medication before initiating NSAIDs. The same argument applies to topical agents. CBT is safe and appropriate for patients with varying levels of pain. We chose CBT over a self-management program given the ability of CBT to address comorbidities that are commonly associated with OA and frequent among Veterans (e.g. depression and insomnia [7,8]) and the Pain Research Informatics Medical Comorbidity and Education (PRIME) Center's extensive experience and expertise in delivering CBT.

To address our objectives, we propose a 2-phase randomized withdrawal trial (RWT) (see Figure 2, section D):

Phase 1: Veterans with knee OA will be randomized to continue NSAIDs or to placebo for 4 weeks. This double-blind phase will enable us to infer whether placebo is non-inferior to continued NSAID use.

Phase 2: At week 4, subjects in the NSAIDs group will continue NSAIDs. Those on placebo will stop taking the placebo and participate in a 10-week CBT program. The second phase will allow us to infer whether CBT is non-inferior to NSAIDs. This adjunctive, non-pharmacologic treatment was chosen because it 1) has already been found to be effective in OA [9-11], 2) can be safely administered to all potential subjects, and 3) can be tailored to benefit patients based on their individual needs. Placebo will not be continued during Phase 2 since it may potentiate the effects of CBT.

The proposal is designed to focus on Veterans who have adapted to their current heath state and is not suitable for subjects with levels of pain warranting escalation of analgesics (Please see Exclusion criteria in D.2). We acknowledge that patients and physicians may be reluctant to stop a medication which they perceive as being effective. In order to maximize enrollment, we will recruit subjects for whom a trial of NSAID

discontinuation is most important: 1) subjects who continue to have symptoms despite regular uses of NSAIDs and 2) subjects at increased risk for NSAID-related toxicity (detailed in D.2).

To the best of our knowledge this will be the first trial to examine the effects of withdrawing NSAIDs. The study design is innovative in that it will definitively answer whether physicians should attempt to withdraw NSAIDs in patients who are comparable to those meeting the eligibility criteria described in this proposal. If positive, the data generated from the study may empower both physicians and patients to try safer treatment alternatives for knee OA. This project will address the VA's commitment to improve care for Veterans with chronic pain as well as those with limited access to VA onsite services. The trial will be supported by the VA Connecticut Healthcare System (VACHS) PRIME Center. The proposed team of investigators includes experienced health services researchers, with expertise in OA, pain, CBT, and cost-effectiveness studies (see section C).

B. BACKGROUND

B.1 Impact of Knee OA: Knee OA is the most common cause of knee pain and lower extremity disability in older adults [12]. Veterans have an even higher prevalence of OA compared to non-Veterans [1] and over half report being limited in their daily activities because of joint symptoms [13]. Persons with knee OA have significantly lower quality of life scores in all domains compared to age-matched controls [14]. This disease affects approximately 27 million Americans and the current annual healthcare cost estimates for knee OA range between 68 and 95 billion dollars. Annual costs due to absenteeism are approximately 10.3 billion US dollars [15]. The impact and costs related to knee OA are expected to rise exponentially as the number of older adults in the population increases. The impact of OA in Veterans is not limited to older adults. Rates are 26% higher in service members age 20 to 24 than in the general population and troops over the age of 40 are more than twice as likely to develop OA as civilians [16]. Injuries are likely to play a role in the pathogenesis of OA in younger Veterans returning from Iraq and Afghanistan. Research studies focused on developing safe approaches to managing pain in this younger population are particularly important given the chronicity of the disease.

B.2 Management of Knee OA: OA is characterized by progressive joint degeneration. At present, there is no cure for the disease nor has any intervention been shown to alter its progression. Medical treatment of OA (which includes both pharmacologic and non-pharmacologic options) is aimed at management of symptoms (pain, swelling and stiffness) and maintenance or improvement of lower extremity function. In general, the effect sizes related to these options are modest [2]. In contrast, total knee arthroplasty is a highly effective treatment option for patients with knee OA [17]. Yet, not all patients want, or are eligible for surgery.

B.3 Efficacy and Toxicity of NSAIDs: Short-term trials have demonstrated that NSAIDs are more effective at decreasing knee pain in OA compared to both placebo and acetaminophen [18]. However, the effect sizes are small and there are no data to support the use of NSAIDs beyond 3 months [19]. A meta-analysis focusing on the efficacy of NSAIDs for knee OA found that subjects improved by 15.6% (as measured by changes in pain severity using a visual analogue scale) after 2 to 13 weeks. The corresponding effect size, in a random effects model, was 0.3 (0.2-0.4) [4]. Maximum NSAID related benefits occur within 1 month and there is no proven difference in knee OA pain at 1 year between NSAIDs and placebo [5].

Despite the limited data supporting their use, NSAIDs are the most commonly prescribed medications for OA. More than 100 million prescriptions are written for NSAIDs in the US each year. This dramatic figure does not account for the number of OTC NSAIDs used. The widespread use of NSAIDs for OA warrants careful scrutiny because of the known significant toxicity associated with this class of medications. NSAIDs increase the risk of gastrointestinal ulcer disease and hemorrhage, acute renal failure, serious cardiovascular events (including stroke and myocardial infarction) and worsening of preexisting heart failure [20,21]. Complications related to long-term NSAID use result in approximately 103,000 hospitalizations and 16,500 deaths annually. The number needed to harm in Veterans for an NSAID-related death is 105 for a gastrointestinal hemorrhage, 11 for a myocardial infarction, and 20 for a stroke [22]. That is, only 20 NSAID-users would have to suffer a NSAID-related stroke to result in 1 additional death within 30 days. Forty-three percent of Veterans are considered to be at high risk of NSAID-related complications, and yet adherence to evidence-based guidelines for safer prescription of NSAIDs is low (27%) in the VA [23].

B.4 CBT and Pain: CBT is the most commonly cited psychological alternative to more traditional medical and rehabilitation approaches to chronic pain management, and has demonstrated efficacy for reducing pain and improving function in persons with a broad spectrum of conditions [24]. CBT is informed by a theory of chronic pain that hypothesizes that patients' idiosyncratic beliefs, attitudes and coping resources play a central role in determining their experiences of pain [25]. The overarching goal of CBT is to assist the patient in the development of an adaptive problem-solving, self-directed approach to pain management based on a conceptualization of pain as controllable and a personal attitude of self-efficacy and self-control. CBT is a structured and goal-oriented therapeutic approach that can be delivered in either small group or individual sessions. During therapy, a range of cognitive pain coping skills (e.g., challenging unhealthy thoughts, development of positive coping self-statements) and behavioral strategies (e.g., activity pacing, mental relaxation and other stress reduction) are taught. Progress toward overall treatment goals and pain coping skill practice are encouraged through the development of intersession homework assignments. Naylor et al [26] recently published the results of a trial designed to examine the effects of CBT on NSAID and opioid usage. In this trial, after 11 weeks of group CBT, 51 subjects with chronic musculoskeletal pain were randomized to a therapeutic interactive voice response program and 25 subjects were randomized to receive usual care. Between-groups analysis demonstrated significant reductions in opioid use at 8 months among subjects randomized to the experimental arm. NSAID use was lower after 4, but not after 8 months of follow-up.

B.5 CBT and Knee OA: Experimental studies have demonstrated that CBT is an effective treatment for patients with OA. Keefe et al [9] conducted a 3-arm, 10-week RCT in which patients with knee OA were randomized to CBT, arthritis education, or usual care. The CBT program included weekly group sessions which trained participants to recognize and reduce irrational cognitions and to adopt attention diversion and activity modification. The education intervention included weekly sessions in which participants were provided with detailed information about knee OA. The trial demonstrated that patients receiving pain coping skills training had significantly lower levels of pain and psychological disability post treatment than patients receiving arthritis education or standard care after adjusting for age, gender, obesity and pretreatment scores. Participants in the pain coping skills training group who reported increases in the perceived effectiveness of their coping strategies were more likely to have lower levels of physical disability post-treatment. After 6 months, participants randomized to CBT continued to have lower levels of psychological and physical disability than those who had received education and usual care.

Calfas et al [27] conducted a trial to compare CBT and education in OA. CBT was delivered in 10 weekly group sessions and education included 10 weekly didactic lectures given by health professionals. After one year, subjects in both groups demonstrated significant improvements in depressive symptoms, quality of well-being and pain; however, there were no between-group differences. In a recent trial examining the closely associated variables of sleep disturbance and pain, CBT improved sleep and decreased pain in subjects with OA, whereas subjects randomized to an attention control reported no improvements in either condition [7]. In addition, a meta-analysis found that CBT has significant beneficial effects on pain, anxiety, depression and coping skills in patients with arthritis [28]. This review concluded that there was strong evidence to support an incremental benefit of CBT over and above standard medical care.

There are also some indirect data to suggest that the proposed strategy may be cost effective for the VA. Cronan et al [29] found that OA patients receiving interventions emphasizing self-management incurred significantly fewer costs than those randomized to routine care after 3 years of follow-up. Similarly, Mazzuca et al [30] found that a self-care program reduced cost in knee OA by decreasing the number of primary care visits in the year following completion of the intervention. The proposed trial may result in decreased utilization of services related to treatment for OA; however, we expect that cost savings will result primarily from decreased NSAID-related hospitalization rates.

B.6 Appeal of Telephone-Based Strategies: Telephone-based interventions have the potential to greatly expand delivery of care at an affordable cost to Veterans with limited access to outpatient clinics (due to geographic, financial, or health-related barriers). This is especially true for older adults with OA living in regions with poor public transportation. Telephone-based behavioral interventions can frequently be delivered at lower cost than face-to-face interventions, and are less impeded by the time and space constraints inherent to many subspecialty clinics within the VA.

B.6.a Telephone-Based Programs for OA: Previous controlled studies have demonstrated that telephone-based programs can improve functional status in patients with OA. Rene et al [31] found that a telephone-administered educational intervention improved patients' functional status. In a separate study, Maisiuk et al [32] demonstrated that treatment counseling provided over the telephone every 2 weeks for 5 weeks and then monthly for 6 months resulted in greater improvement in arthritis-related health status and fewer medical visits compared to usual care. The recently published Self-Management of Osteoarthritis in Veterans Study demonstrated that a telephone-based self-management intervention significantly reduced pain in a non-treatment seeking sample of Veterans with OA [33]. The treatment was delivered monthly, over 12 months using short telephone contacts averaging 9 minutes per call supplemented with audio and written materials. Given the success of this treatment, we have retained many of its elements in the proposed study. Specifically, the treatment in the proposed study emphasizes the use of pain management skills such as relaxation, reframing of pain-related cognitions, sleep hygiene, regular exercise, goal setting and skill practice to encourage skill use and mastery. We have, however, opted for more frequent and longer (~30-45 minute) sessions in order to effectively deliver a comprehensive CBT program.

B.6.b Telephone-Administered CBT: Several experimental studies have demonstrated that CBT can be successfully administered over the telephone. Lovell et al [34] found that telephone-administered CBT was just as effective as face-to-face CBT in treating subjects with obsessive compulsive disorder. Taylor et al [35] also demonstrated the efficacy of telephone-administered CBT in subjects with this disorder. Mohr et al [36] found that telephone-administered CBT was more effective than telephone-delivered supportive emotion-focused therapy in treating depression amongst patients with multiple sclerosis. DuHamel et al [37] demonstrated that telephone-administered CBT was effective at treating posttraumatic stress disorder in cancer survivors.

B.7 Randomized Withdrawal Trials: While the traditional RCT is the most commonly used design to assess treatment efficacy, the large number of Veterans with knee OA already using NSAIDs, the expected number of drop-outs in a long-term pain study, the safety concerns related to initiating long-term use of NSAIDs in an experimental setting, and the expected increased use of co-therapies with time, warrant consideration of an alternative approach. Amery and Dony first proposed the RWT design as a method to examine the long-term efficacy of non-curative treatment options in 1975 [38]. In contrast to the classic RCT, the RWT randomizes subjects currently using the intervention to continued use or to placebo. This approach is particularly useful for examining the efficacy of symptomatic (i.e. non-curative) treatments when prolonged use of placebo and expected number of drop-outs is likely to threaten the internal validity of the trial. The RWT is also a practical method of obtaining evidence to support or refute the continued use of medications which are already widely prescribed despite the lack of definitive evidence justifying their use.

A systematic review of RWTs evaluating analgesics [39] and a second paper utilizing computer simulation models [40] concluded that the RWT is an efficient design requiring sample sizes of 20% to 50% of those in classic RCTs. The required sample sizes are smaller because of the greater homogeneity in the study population. Carryover and withdrawal syndromes, important limitations of this approach, are not relevant for the proposed study, as NSAIDs have relatively short half-lives and unlike opioids do not cause withdrawal symptoms (apart from recurrent pain) upon discontinuation.

A Medline search on October 27, 2011 of the following Medline terms (text words: discontinuation trial or withdrawal trial and MESH terms: analgesics or pain or arthritis or NSAIDs) revealed 7 published RWTs [41-47]. Six used an enriched enrollment randomized design, in which patients who respond to the study drug during the initial phase were subsequently randomly assigned to continue the study drug or to placebo. All were designed as superiority trials and demonstrated significant differences between the active drug and the placebo. The eighth study is the most relevant to the RWT described in this application. In this study, Cibere et al [42] randomized 137 subjects currently using glucosamine (a widely available neutraceutical used for arthritis) to continued use of glucosamine versus placebo. The authors chose to use a RWT design because of the prevalent use of glucosamine and the assumed, albeit unproven, long-term effectiveness of the compound. After 6 months, the active neutraceutical was not found to be more effective than placebo. However, because the study was designed as a superiority trial, it cannot conclude that there is no difference between placebo and glucosamine. For this reason the proposed trial is designed as a non-inferiority trial.

B.8 Non-Inferiority Trials: Because the clinical question of interest is to determine whether placebo + CBT <u>is no worse</u> than continued NSAID use, a superiority trial is not well-suited to this proposal. A superiority trial

would not allow us to determine whether Veterans who discontinue NSAIDs do not experience more pain compared to those who continue NSAIDs ─ even if well powered and negative [48]. While superiority trials, which fail to reject the null hypothesis, are frequently interpreted as negative (i.e., no difference between the 2 groups), they should be interpreted as indeterminate (uncertain) [48]. A non-inferiority trial is appropriate in this context because the new strategy under investigation is safer than the current widespread long-term use of NSAIDs for knee OA [49]. We acknowledge, however, that there are important issues to be considered in designing a non-inferiority trial, including:

1. Assay sensitivity: We will take several precautions to reduce the factors that can limit assay sensitivity (i.e., the ability of a trial to demonstrate a real difference between the 2 arms if one truly exists). We will include a run-in period to ensure that subjects respond to and are able to tolerate the study drug. We will include measures to enhance CBT treatment fidelity (see D.16). We will measure the primary outcome and adherence weekly, employ a well-validated primary outcome measure, and use both an intent-to-treat (ITT) and a "completers" or per protocol analysis (PP) as justified below. These design features are recommended to minimize biases towards the null [49].
2. Choice of the non-inferiority margin: The margin of non-inferiority will be pre-stated and informed by both clinical judgment and the expected differences between study arms [49].
3. Analyses: Because the ITT approach analyzes all subjects according to their initial group assignment, including those who do not complete the protocol, it tends to bias toward making the results look similar across groups. Consequently, we will perform both ITT and PP analyses. Experts recommend that objectives in non-inferiority trials be met by both approaches [49].

B.9 Study Drug: Though it would be ideal for subjects randomized to the active study drug to continue their current NSAID, having the VA pharmacy formulate multiple different active drugs and maintaining the blind would be unwieldy and cost prohibitive. Given that studies have failed to demonstrate any significant differences amongst NSAIDs in treating subjects with OA [18] the use of a single active drug in this protocol is justified. However, we acknowledge, that individual patients may respond differently to specific NSAIDs. To ensure that lack of a response or intolerance to meloxicam does not bias our results towards the null, we will include a 2-week run-in period where study subjects will replace their NSAID with the study drug (see D. 6). The duration of the run-in period was chosen based on data demonstrating that patients with OA respond to meloxicam by 2 weeks [50].

The decision to use meloxicam as the study drug was based on local practices and safety concerns [50,51]. At the VACHS, the most commonly prescribed NSAID is meloxicam 15mg orally once daily. Of the 8,514 orders for NSAIDs written between October 2009 and October 2010, 1,975 were for meloxicam 15mg (only 6 were for meloxicam 7.5mg) and most of the remaining prescriptions were for varying doses of naproxen and ibuprofen. Reliable data on the most commonly used OTC NSAIDs are not available. RCT data demonstrate that the efficacy of meloxicam is comparable to other NSAIDs in subjects with knee OA [52]. A trial conducted by Yocum et al [50] found that meloxicam was as effective, but better tolerated than diclofenac, in subjects whose previous NSAID was withdrawn. The latter study provides particular support for the use of this agent in our trial. In terms of safety, meloxicam inhibits Cox-2 more than Cox-1 and has been shown to have improved gastrointestinal tolerability compared to other NSAIDs. In a systematic review of clinical trials, serious gastrointestinal events (defined as perforation, ulceration or bleeding) was 0.2% in subjects receiving meloxicam, 1.2% in subjects receiving piroxicam, 0.6% in subjects receiving diclofenac, and 2.1% in subjects receiving naproxen [52].

B.10 Importance of this Project to Veterans: Knee OA is now recognized as a major health problem. It is the number one cause of lower extremity disability and has significant deleterious effects on quality of life [1]. While there are numerous therapies available for knee OA, most have limited efficacy [2]. Of particular concern is the widespread use of NSAIDs and their associated increased rates of morbidity and mortality. Veterans, as a group, are at particularly high risk for both gastrointestinal and cardiovascular NSAID-induced complications.

The proposed study is especially appealing because: 1) it may decrease drug-related morbidity and mortality; 2) we now recognize that access to VA health services is a significant barrier for at least one third of the 3 million Veterans living in rural areas; 3) Veterans with knee OA are often among those likely to have difficulty with transportation because they are older and suffer from pain and subsequent limited mobility; 4) telephone-

administered programs have been shown to benefit patients with knee OA; 5) if successful, implementation of this strategy will be greatly facilitated by the vast telehealth expertise already in place within the VA; and 6) this program may result in significant cost savings for both Veterans (decreased co-pays and transportation costs) and the VA (decreased hospitalizations due to NSAID-induced toxicity). This work will also provide the VA with data enabling prioritized, value-based health care, where treatment strategies offering greater clinical benefit at equal or reduced cost could be supported or expanded, while lower value strategies could be restricted or have increased cost-sharing, resulting in amplification of health benefits without increased health expenditures [53].

C. INVESTIGATORS' QUALIFICATIONS

PRIME Center investigators have an established reputation for the development of models for psychological interventions for chronic pain, for the development of measures of pain outcomes and process, for the conduct of high quality RCTs of psychological interventions, and for the evaluation of published research in this area. Recently completed is a Clinical Science R&D Merit project of the efficacy of tailored CBT for chronic back pain that supports the efficacy of a pain coping skill training approach for Veterans with chronic musculoskeletal pain. Expanded, proactive methods for recruitment similar to those proposed in the current trial have recently been approved by our local IRB.

Liana Fraenkel, MD, MPH is Associate Professor of Medicine at Yale University, Chief of Rheumatology at the VACHS, Co-Director of the VA Connecticut Bone and Joint Clinic, and a research scientist at the VACHS Clinical Epidemiologic Research Center (CERC, John Concato PI), and a Core Investigator of the VACHS PRIME Center (Robert Kerns PI). She has secured career development and project support over the past 12 years from the VA Health Services and Research Department. Dr. Fraenkel has received funding as PI for 3 Merit Review projects. She has previously conducted clinical studies in OA, including a pilot RCT of a decision support tool for knee OA treatment within the VA, and is currently supervising a rheumatology research fellow conducting an RCT to determine if ultrasound-guided intraarticular corticosteroid injections are more effective than sham ultrasound injection.

Alicia Heapy, PhD is a doctoral level psychologist (8/8ths at VACHS) who has served as a co-investigator on a number of funded projects investigating the efficacy of psychological intervention for the management of chronic pain. She is the Associate Director and a Core investigator of the PRIME Center and an Associate Research Scientist at the Yale University School of Medicine. She has extensive expertise in CBT and particular experience in adapting manualized psychological treatments to address chronic pain complaints in patients with co-morbid chronic conditions. Dr. Heapy has also used telephone and interactive voice response technology to increase the availability of empirically-validated psychological treatments for Veterans with chronic pain who are geographically, medically, or financially limited in their ability to travel to the VA for treatment. She is currently the PI for an HSR&D funded IIR RCT of a CBT intervention for Veterans with chronic low back pain.

Cynthia Brandt, MD is Director of the Informatics Core for the VACHS PRIME Center (8/8ths at VACHS). She is a staff physician at VACHS, Associate Professor at Yale University School of Medicine, Director of the Yale Center for Medical Informatics and Director of the Medical Informatics Core of the PRIME Center. Dr. Brandt has been extensively involved with clinical research database development and research, with a particular research focus on metadata management. She is PI for several VA grants, including West Haven's postdoctoral training program in Medical Informatics and the HSR&D funded Women Veteran's Cohort Study, and site PI at West Haven for the Consortium for Informatics Health Research grant. She performs research on issues such as the management of clinical vocabularies used in clinical research databases and the creation and use of study-specific and disease-specific databases that store focused and carefully defined sets of data. As a result, Dr. Brandt has extensive experience working with electronic medical record (EMR) systems including the VA EMR data.

Joseph Goulet, PhD, MS is Director of the Biostatistics and Methodology Core for the PRIME Center and Associate Research Scientist in the Department of Psychiatry at the Yale University School of Medicine (8/8ths at VACHS). He is highly experienced in collaborating with biomedical researchers in the design, analysis and interpretation of VA data. His research interests are in the development and application of statistical methods for the analysis of observational data; clustering algorithms; and longitudinal analysis. He has published on

genetic epidemiology, psychiatry, HIV, and pain management in terminal care and is the lead statistician on other PRIME Center behavioral RCTs.

Robert Kerns, PhD is VHA National Program Director for Pain Management, Director of the VACHS PRIME Center, and Professor of Psychiatry, Neurology and Psychology at Yale University (8/8ths at VACHS). He is widely recognized as a leading expert in the field of pain and pain management within the broader context of clinical health psychology and behavioral medicine. In his role as National Program Director for Pain Management, he has broad responsibilities for policy development, implementation, and oversight for the VHA National Pain Management Strategy. Of particular relevance to the proposed project, he has published on the processes of engaging persons with arthritis in self-management approaches to pain and disability.

Francis Keefe, PhD is Professor in the Department of Psychiatry and Behavioral Sciences and a member of the Cancer Prevention, Detection, and Control Program of the Duke Comprehensive Cancer Center. Dr. Keefe directs an active clinical research program concerned with the behavioral assessment and treatment of patients having acute and persistent pain and played a key role in the development of clinical pain services and pain research programs at Duke Medical Center. For 20 years, he directed the Pain Management Program and was a leader in the development of Duke Medical Center's multidisciplinary pain programs (both out-patient and in-patient). Dr. Keefe has developed and refined a number of treatment protocols for persistent pain conditions (e.g. cancer, arthritis) including spouse- and partner-assisted pain coping skills training interventions. He served as the Clinical Psychology Field Editor for the journal PAIN from 1999 to 2010.

Lisa Gale Suter, MD is an attending rheumatologist at the VACHS and VA Connecticut Bone and Joint Clinic, and a research scientist at the VACHS CERC and PRIME Center. She is also an Assistant Professor in the Department of Internal Medicine at the Yale University School of Medicine. She has secured continuous independent funding from both NIH and the Arthritis Foundation to develop and perform cost-effectiveness research in rheumatology since 2006. She has published several articles on cost-effectiveness in musculosketelal medicine using a variety of decision analytic methods. Her work on the cost-effectiveness of adding magnetic resonance imaging to early RA management has been recently published in Archives of Internal Medicine [54]. Dr. Suter is also a collaborator on the Osteoarthritis Policy Model, a NIH-funded state-transition simulation model of the natural history and management of knee OA (Elena Losina PI, Brigham and Women's Hospital, Boston, MA). Dr. Suter's novel work identifying optimal candidates for arthroscopic partial meniscectomy was selected as one of the 2009 Top 10 Arthritis Advances by the Arthritis Foundation.

Doug Leslie, PhD is Professor in the Departments of Public Health Sciences and Psychiatry at the Penn State College of Medicine. He is an economist whose research focuses on the field of health economics and health services research. His areas of study have included the effects of managed care on service use and costs, factors affecting access to and the quality of health care, adherence to treatment guidelines, and the pharmacoeconomics of prescription medications. Dr. Leslie has extensive experience using VA administrative databases to track patterns of health care service use and costs. He has over 60 peer-reviewed publications and is the PI of 2 Federally-funded grants to use large administrative claims databases to examine patterns of service use and costs over time and across states. Dr. Leslie has established working relationships with PRIME Center investigators and has been working with Drs. Brandt and Goulet on the Women Veterans Cohort Study (HSR&D funded IIR) since November 2007.

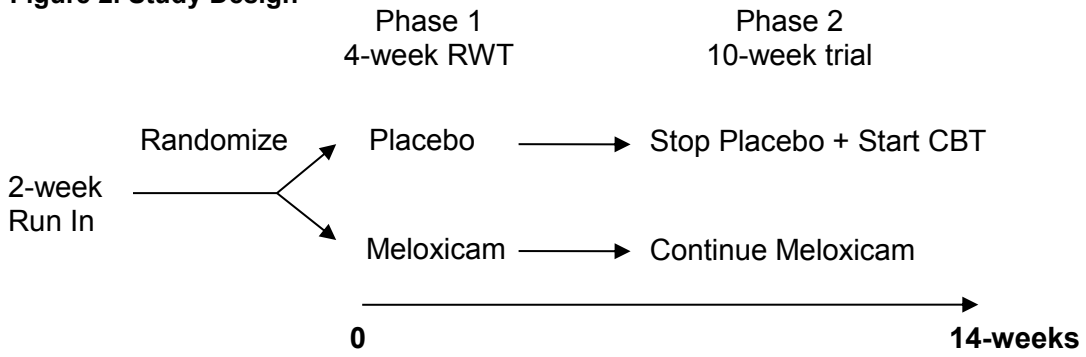
Sam Poon, MD is a Staff Rheumatologist at the Roger Williams Medical Center and the VA Providence Medical Center. He will meet with subjects to describe the study and will obtain written consent at this neighboring site.

Robert Swift, MD, Ph.D. is the Associate Chief of Staff for Research at the VA Providence Medical Center. He is a psychiatrist and pharmacologist with more than 20 years of experience conducting controlled clinical trials. He has been a site PI or overall PI for clinical trials with naltrexone, antidepressants and second generation antipsychotics in outpatient clinical research settings. He has also been a site PI for the NIAAA COMBINE Alcoholism Treatment Trial and other NIH and industry sponsored multi-site clinical trials. Moreover, he has had experience with multi-site VA studies managed by the VA Central IRB.

D. METHODS

Overview: Participants will participate in a 2-week run-in period where all subjects will replace their current NSAID with the study drug (meloxicam 15mg per day). Those who remain eligible at the end of the run-in period, will participate in a 4-week, double-blind, placebo-controlled, non-inferiority RWT. After 4 weeks, subjects in the meloxicam arm will continue on the study drug. Subjects in the placebo arm will stop the placebo and participate in a 10-week CBT program (Figure 2).

Figure 2. Study Design



Aim 1: To determine whether placebo is non-inferior to continued NSAID use: 680 subjects will be enrolled into a 2-week run-in period where they will stop their current NSAID and start taking the study drug (meloxicam 15mg per day). Those who remain eligible after the run-in period will be randomized to continued meloxicam use versus placebo for 4 weeks.

Aim 2: To determine whether CBT is non-inferior to continued NSAID use: After 4 weeks, subjects in the meloxicam arm will continue on the study drug. Those in the placebo arm will stop the placebo and participate in a 10-week CBT program.

D.1 Subjects: Participants will be drawn from Veterans with knee OA currently enrolled in the VACHS and the Providence VA Medical Center. Both centers serve Veterans with similar demographics; approximately 85% Veterans are White, 14% are Black, 0.3% are Pacific Islanders, 0.2% are Native American, and 0.1% are Asian. Twelve percent describe themselves as being Hispanic. As of 2012, West Haven had 1987 women enrolled: 38% between the ages of 18 and 44, 37% between the ages of 45-64, and 25% over the age of 65. The corresponding numbers of women at the Providence VA are: Total = 1098: 31% between the ages of 18 and 44, 39% between the ages of 45-64, and 29% over the age of 65. We will oversample women during the recruitment phase by ensuring that up to 50% of the opt-out letters sent are to women. The same approach will be used to improve representation of minorities.

D.2 Eligibility

Subjects will include those for whom a discontinuation trial of NSAIDs is most appropriate: 1) Veterans with knee pain despite NSAID use and/or 2) Veterans at relatively higher risk of NSAID toxicity [55-59] as ascertained by meeting 1 or more of the following 4 criteria*:*

- Answer affirmatively to the question: “Do you have some knee pain on most days over the past 3 months?”
- Have 1 or more risk factors for NSAID-induced nephrotoxicity (age greater than 60 years, atherosclerotic cardiovascular disease, current diuretic use, chronic renal insufficiency, congestive heart failure (New York Heart Association class I–II. Note, Class III and IV are excluded).
- Have 1 or more risk factors for NSAID-induced gastrointestinal toxicity (history of peptic ulcer disease, age > 65 years, concurrent use of daily ASA or corticosteroids), and are currently on a gastro-protective agent.
- Have 1 or more risk factors for NSAID-induced cardiovascular toxicity (prevalent cardiovascular disease, hypertension, hypercholesterolemia, diabetes, smoking, family history of early heart disease or age greater than 55 years for women).

In addition, subjects must:

- Be age 20 years or older. While the usual cut off for knee OA is approximately 40 years, we chose to lower the age cutoff as younger Veterans have a higher than expected risk of OA (see B.1).
- Have radiographic evidence of knee OA reported in the VistA electronic system.
- Be using an NSAID (other than daily ASA) for knee pain on most days of the month for at least the past 3 months.
- Be able to understand and speak English and have a telephone.
- Be willing to engage in a CBT program, to discontinue (or replace) their NSAID, and to restrict co-therapies to acetaminophen for 14 weeks.

Exclusion criteria are:

- Subjects desiring escalation of analgesics for their current level of knee pain as determined by endorsement of the following statement: "Is your knee pain bad enough that you want to talk to your doctor about taking stronger pain medications?"
- Current use of opioids and/or Celebrex.
- Current use of an NSAID (not including ASA) for a painful condition *in addition to* knee OA.
- Contraindications to chronic NSAID use: current use of warfarin or antiplatelet agent other than ASA, allergy to any NSAID, active upper gastrointestinal ulceration in the previous 30 days, upper gastrointestinal bleeding in the past year, history of gastroduodenal perforation or obstruction, cardiovascular event within the past 6 months (myocardial infarction, cerebrovascular event, coronary-artery bypass graft, invasive coronary revascularisation, or new-onset angina), severe congestive heart failure (New York Heart Association class III–IV), evidence of serious anemia, hepatic, renal *(including nephrotic syndrome),* or blood coagulation disorders, and pregnancy.

Though we are proposing a RWT – and thus will not be initiating NSAID therapy – it would not be appropriate to continue NSAIDs (even when prescribed) in high-risk patients. We acknowledge that these exclusion criteria limit generalizability, but we feel they are justified to ensure subjects' safety.

- Previous hyaluronic acid knee injections (within 6 months) or corticosteroid knee injections (within 3 months).
- Scheduled knee hyaluronic acid or corticosteroid injections, arthroscopy, or knee surgery.
- Co-morbid conditions that include the following: known other causes of arthritis (infectious arthritis, rheumatoid arthritis, connective tissue disease, gout, pseudogout, or psoriatic arthritis), peripheral neuropathy or cardiopulmonary disease that limits walking more than knee pain, bone metastases or Paget's disease involving the lower extremities, and history of drug or alcohol abuse within the past 2 years, bilateral knee replacements or knee pain in the replaced knee only.
- Current involvement in litigation or receiving workmen's compensation.
- Hearing, cognitive impairment or mental illness, as determined by chart review that would preclude participation in a CBT program.
- For Women of Childbearing Age: Must not currently be pregnant, agree to avoid getting pregnant during the course of the study and should inform the study team if pregnancy occurs at any time during study participation.
- **D.3 Screening Procedures:** We will request the appropriate HIPAA and informed consent waivers to perform the searches described below. We have obtained waivers for similar screening and recruitment approaches in previous and ongoing studies.

D.3.a RDW/CDW Search: We will identify potential Veterans for inclusion from available EMR data in RDW/CDW. The VA RDW includes patient clinical data including demographics, encounters, vital signs, health factors and radiology reports. We will extend previously applied methods of information retrieval, concept indexing, and mapping to identify potentially eligible subjects for the study. All Veterans 20 years or older from VA CT and the Providence VA Medical Center with a radiology report performed during 01/01/2007-12/31/2011 that contains text indicative of knee OA will be identified using simple text searches. We have used a similar approach previously for the Lung Cancer Tracking System developed at the VACHS. This approach uses

radiology reports to identify patients with lung nodules using natural language processing techniques for case management purposes. We will then identify Veterans in this group to exclude those who are taking medications such as Cox-2 inhibitors (other than meloxicam), warfarin, or antiplatelet drugs other than NSAIDs and ASA within the past 6 months. We will use ICD9 codes and encounter data to further exclude patients with a hospitalization for active upper gastrointestinal ulceration in the previous 30 days, upper gastrointestinal bleeding in the past year, gastroduodenal perforation or obstruction at any time, or a cardiovascular event within the past 6 months (myocardial infarction, cerebrovascular event, coronary-artery bypass graft, invasive coronary revascularisation, new-onset angina or congestive heart failure).

D.3.b Chart Review: For Veterans who remain potentially eligible, we will perform a focused EMR review to check for evidence of serious anemia, hepatic, renal, or blood coagulation disorders; previous hyaluronic acid knee injections (within 6 months) or corticosteroid knee injections (within 3 months); co-morbid conditions that include the following: known other causes of arthritis (infectious arthritis, rheumatoid arthritis, connective tissue disease, gout, pseudogout, or psoriatic arthritis), peripheral neuropathy or cardiopulmonary disease that limits walking more than knee pain, bone metastases or Paget's disease involving the lower extremities; history of drug or alcohol abuse within the past 2 years; bilateral knee replacements or knee pain limited to a single replaced knee; current involvement in litigation or receiving workmen's compensation; and mental illness, hearing or cognitive impairment that would preclude participation in a CBT program.

D.3.c Recruitment: We will use several methods of recruitment to maximize enrollment.

- **Mailings:** Veterans meeting initial eligibility criteria will be sampled in blocks of 25-50 and mailed a letter informing them of the purpose of the study. The letter will notify the potential subjects that they will be telephoned by the project coordinator and will offer them the opportunity to refuse this contact by calling an answering machine and leaving a message. The project coordinator will telephone all patients who do not "opt out." To minimize any intrusion on Veterans' privacy, the project coordinator will be trained by the PI on how and when to contact potential subjects. Specifically, we will only telephone people during the day or early evening (7:00-8:00). We will not contact people during dinner (5:30 to 7:00). If someone other than the participant answers the telephone, we will not share any personal health information with the person who answers. We will attempt to reach each subject up to 3 times. Subjects will be assured that their participation is voluntary, confidential and that a decision to not participate in the study will in no way affect the care they receive. The PI has used the same procedures in 2 studies with no adverse outcomes or protest from contacted patients.

Telephone Screen: Those veterans who do not opt out will be telephoned to verify the remaining eligibility criteria: able to speak English; have a telephone; be using an NSAID, either by Rx or OTC, for knee pain (and not for any other painful condition) on most days over the past 3 months; do not desire escalation of analgesics; do not have scheduled knee hyaluronic acid injections, corticosteroid injections, arthroscopy, or knee surgery; be willing to engage in a CBT program, discontinue or replace their NSAID and restrict co-therapies to acetaminophen up to 3 g daily; do not have a hearing or cognitive impairment or mental illness precluding participation in a CBT program. And for women of childbearing age, will verify they are not pregnant, are willing to avoid getting pregnant during study participation, and agree to a pregnancy test at time of consent. Ambiguous data retrieved during the VistA or chart screen will be clarified with subjects during the telephone screen.

Physician Referrals: Study Coordinator will inform Primary Care Doctors (PCPs), nurses, and health technicians in the outpatient clinics at VA CT and Providence VA Medical Center as well as coordinators of the MOVE program and Patient Education about the current study, and ask that they either (1) give out a flier to all patients, age 20 or older with knee pain, so they can call Study Coordinator for more study information if interested in participation or 2) discuss the study with knee osteoarthritis patients who meet eligibility criteria and have their interested patients sign a note that states their willingness to be contacted by telephone about the current study and asks for their contact information. This note will also include the study team's telephone numbers in case patients would like to verify that this is a VA research project. The same recruitment strategy will be employed at the Providence VA Medical Center with the exception that study fliers will not be given out to patients because it will require them to make an out-of-state phone call.

Study Fliers: Study fliers will be posted in all approved areas around the West Haven VA In addition, these fliers will be left near check-in desks at all primary care and specialty clinics.

D.4 Informed Consent: At VACHS, the project coordinator will describe the study and set up a clinic appointment for subjects who are eligible and interested in participating. The clinic appointment will be made at a time convenient for each patient. During the clinic appointment, the study procedures will be described in detail and the project coordinator will obtain written consent. The purpose of the study, all study procedures (including the run-in period), the process of randomization, the procedures (discontinue NSAID, be randomized to study drug versus placebo, possibly participate in a CBT program after 4 weeks, keep a daily medication diary, and provide outcome data each week), expected risks, expected benefits, alternative therapies, use of research results, special circumstances, and subjects' rights will be discussed with each subject. The participants will also be asked to sign a separate consent for audio recording of CBT phone sessions so that they do not have to return back to the VA at a later date should they be assigned to CBT in phase 2. Female participants of childbearing age will be given a lab slip to get a blood test at the VA laboratory at the time of signing consent form.

The same procedures will be followed at Providence VA Medical Center, except that Dr. Poon, Dr. Swift and/or their research assistant will meet with subjects to describe the study and obtain written consent.

D.5 Run-In Period: Subjects will be asked to participate in a 2-week run-in period. Despite the exclusion of potential subjects, trial run-ins have been shown to enhance a trial's statistical power by decreasing the number of subjects who drop out or do not adhere to the study protocol [64]. A run-in period is especially important in this trial to ensure that we avoid a bias towards the null resulting from poor response to a new NSAID. Because patients are already on NSAIDs, a two-week period is adequate to determine whether they will experience a pain flare-up All subjects (including those currently taking meloxicam) will discontinue their current NSAID and be instructed to take meloxicam 15mgonce a day with breakfast. Subjects will be aware that randomization to either the same active drug or to an identical placebo will occur for those remaining eligible after 2 weeks. Meloxicam can be taken with or without food. However, because some subjects will have been previously instructed to take their NSAID with food, we will instruct subjects to take the study drug with breakfast.

Subjects will remain eligible if after the 2-week run-in period they report having taken meloxicam on 10 or more days, deny developing any AEs to the study drug, deny using arthritis medications for knee pain apart from acetaminophen up to 3 g daily, and do not report worsening of knee pain on a 5-point global impression of change scale (see D.11.b).

D.6 Intervention

D.6.a Capsules: Active meloxicam and placebo capsules (both blue gel) will be supplied by the VACHS Research Pharmacy. The active capsules will include 15mg of meloxicam and the placebo capsules will include excipients only. The active capsules will be indistinguishable from the placebo capsules. Subjects will be instructed to take the capsules once a day. Subjects can opt to either pick up their medications from the VACHS Research Pharmacy or receive them by mail. They will be asked to either mail back unused study medications in a pre-paid, addressed envelope, or return them directly to the Research Pharmacy. Pharmacy will document the study drug lots returned on a dispensing log and will subsequently dispose the remaining drugs accordance with hospital policy.

Subjects randomized to the placebo arm will discontinue study medication (meloxicam) after 4 weeks, while those on the continued NSAID arm will continue meloxicam through Phase 2. Phase 2 meloxicam subjects will follow the same instructions above, with the exception that they will be given the standard meloxicam tablets administered at the VA.

D.6.b CBT: The CBT protocol includes 10 treatment modules delivered over 10 consecutive weeks (outlined in Table 1). We will allow the time frame to be extended by 2 weeks to account for missed sessions. The course of therapy will consist of an introductory module, followed by 8 pain coping skills modules, and conclude with a module emphasizing skill consolidation and relapse prevention. The 8 pain coping skills are: 1) deep breathing and visual imagery, 2) progressive muscle relaxation, 3) physical activity and body mechanics, 4) identifying unhealthy thoughts, 5) cognitive reframing, 6) managing stress, 7) time-based pacing, and 8) sleep hygiene.

We chose to include a module on sleep because knee OA is associated with insomnia and insufficient sleep, sleep problems are extremely common among Veterans, and CBT protocols aimed at improving insomnia decrease pain in patients with OA. Subjects who deny having any sleep problems will be able to choose to spend additional time on one or more of the other skills. These coping skills were selected from a larger collection of possible skills because they were judged by participants in a previous study conducted by Dr. Kerns (Efficacy of Tailored Cognitive-Behavior Therapy for Chronic Back Pain) to be the most important, the most appealing, and the skills they were most confident they could engage in. The CBT protocol incorporates the materials used by Drs. Kern, Otis and Keefe, who are the leading authorities in this field, and modifies them to suit our phone-based program for OA. Given the variable pain levels expected at study entry, pain management will not be the sole focus of treatment. In order to promote engagement, we will adopt a treatment approach that emphasizes general wellness benefits of the skills that are taught. All of the skills can promote general well-being, improved mood, and stress reduction. Additionally, skills such as exercise and proper body mechanics, confer joint protective benefits such as increased muscle strength and flexibility, and can aid in weight management. These activities may also help slow progression of OA. When each skill is presented, participants will be told how the skill can be used during a pain flare and how it can be used to promote maximal physical and/or emotional functioning even in the absence of pain. For example, cognitive reframing techniques are effective in reducing pain catastrophizing that can impede the use of other pain coping skills and diminish mood.

Table 1. Description of CBT Program

Week	Module	Description
1	Introduction and Setting Goals	Education about chronic pain and rationale for CBT. Instruction on daily skill practice goals and free choice goals.
2	Deep Breathing/Visual Imagery	Instructions for diaphragmatic breathing/visual imagery and benefits
3	Progressive Muscle Relaxation	Instructions for progressive muscle relaxation and benefits
4	Physical Activity and Body Mechanics	Instructions for initiating or escalating physical activity level and adopting proper body mechanics
5	Identifying Unhealthy Thoughts	Instructions for identifying negative thoughts and understanding how negative thoughts influence pain, activities and mood
6	Balancing Unhealthy Thoughts	Instructions for countering negative thoughts with coping statements
7	Managing Stress	Instructions for identifying sources/symptoms of stress and learning positive coping strategies
8	Time-Based Pacing	Instruction to pace activities based on time rather than pain
9	Sleep Hygiene	To understand the relationship between sleep problems and pain and the importance of monitoring sleep
10	Relapse Prevention and Planning for the Future	Review of progress made in achieving goals, prepare for pain flare-ups, and develop a future plan for setting goals and keeping healthy

CBT will be delivered in weekly, 30-45 minute, telephone contacts with an experienced licensed psychologist utilizing a treatment manual modified for knee OA based on previously developed and tested materials for chronic pain. The therapist manual includes detailed outlines of the information to be provided to participants for each of the pain coping skill modules.

Before the start of phase 2, participants randomized to CBT will be mailed or given a binder that includes handouts for each of the pain coping skills included in the treatment, a CD to facilitate deep breathing and progressive muscle relaxation, and tracking goals sheets noting the coping skills to be practiced in between each session. In order to foster patient comprehension of the materials, Plain Language Action and Information Network's federal guidelines were used to enhance the handouts' readability and to reduce the mean Kincaid reading level to a 9th grade level.

The format of each session will include: 1) review of intersession goal accomplishment, previously assigned coping skill practice, and other homework; 2) review of previously discussed material; 3) presentation of new material and new skills within a problem-solving framework; 4) in-session practice, covert rehearsal, or discussion of the application of new skills and 5) establishment of specific quantifiable and written intersession behavioral goals, expectations for skill practice, and other homework. Appropriate modifications will be made for the introductory and tenth sessions.

Beginning with the second treatment session, using procedures developed in a previous VA-funded study (Efficacy of Tailored Cognitive-Behavior Therapy for Chronic Back Pain, PI: Kerns), the participants, in collaboration with their therapist, will choose their own goals aimed at improving their quality of life. As participants progress through treatment, they will be encouraged to practice prior session coping skills, especially the ones that are reported to be effective, as well as continue to practice their "free choice" goals that target ways to improve well-being. Session 10 will emphasize skill consolidation and relapse prevention. An explicit review of skills learned during the treatment will be followed by a discussion targeting continued practice and application of skills. Areas of poor adherence to recommendations for skill practice and application will be explicitly addressed. The session will include elicitation of specific concerns about relapse and problem-solving discussion designed to reinforce perceptions of self-efficacy and a commitment to continued skill application.

D.6.c.1 Pilot Testing: We pilot tested the intervention (note that it was 12 weeks) and data collection procedures (see D.12) with 14 participants: mean (SD) age = 68 (10) years; 12 are White; 6 are married. Of the 165 CBT sessions conducted, the average time per session was 33 minutes (range 20-55). Subjects were forthright when they had only partially accomplished their homework, and were able to brainstorm barriers to improve adherence. The subjects seemed appreciative of the one-on-one time given to them and the opportunity to practice skills that might alleviate their knee pain.

The baselines interviews required between 14 and 29 minutes and the follow-up interviews between 9 and 15 minutes to complete. The mean (SD) WOMAC pain score (possible range 0-20) was = 7.3 (5.9) at baseline and 2.8 (2.9) at week 12. The mean (SD) ratings of the skills taught (rated on a 5-point scale 0 = Not at all and 5 = Very Helpful) are provided in Table 2.

Table 2. Participants' Ratings of the Helpfulness of the Skills Taught

Skill	Identify Knee Pain Precipitants	Food Diary	Exercise Plan	Relaxation	Identify Unhealthy Thoughts	Change Unhealthy Thoughts	Pace Activities	Stress Management	Sleep Hygiene
Mean (SD)	4(1)	4(2)	4(1)	5(1)	4(2)	4(1)	4(1)	4(2)	3(2)

The mean (SD) goal attainment scores [0 = Did not work at all on goal(s) to 10 = Completed goal(s)] for each subject are provided in Table 3.

Table 3. Goal Attainment Scores per Pilot Subject

ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Mean (SD)	5(2)	8(3)	8(2)	8(3)	2(2)	6(2)	8(2)	4(2)	6(1)	7(3)	7(2)	4(3)	5(1)	9(1)

All 14 rated the amount of information presented as "Just right" (options: Too much, Not enough, Just right). Eleven rated the length of the calls as "Just right", 2 as "Not enough" and 1 as "Too long" (options: Too long, Too short, Just right). 7 participants stated that they were "Very motivated" to continue practicing/implements

learned skills, 4 stated that they were “Moderately” motivated, 3 “Somewhat”, 2 “A little” and 1 was “Not at all” motivated. Thirteen responded that they would recommend the program to another person with knee pain (Yes/No).

D.7 Randomization and Allocation Concealment: An independent research associate not otherwise affiliated with the study will generate a computer generated randomization code. Subjects will be randomly assigned to the intervention or control group in a 1:1 ratio. Randomization will be stratified by baseline knee pain intensity (≤ 8 vs > 8 on the WOMAC knee pain subscale). The cut-off point was chosen based on NSAID RCT outcome scores at 12 weeks [72]. For subjects with bilateral symptoms, the most painful knee will be chosen as the study knee. Blocking will be used within each of the 2 groups to maintain balanced treatment assignment across both sites. We will use variable block sizes ranging from 2 to 6. For the West Haven patients,the randomization code will be forwarded to the VACHS Research Pharmacy and will be used to label the study medication bottles. Random treatment assignments will be placed in numbered (so that all envelopes can be accounted for at the end of the study) opaque envelopes. Providence VA Pharmacy will be also be forwarded the randomization code for their own patients and label the study medication bottles accordingly.

D.8 Blinding: The study personnel having direct contact with subjects, subjects, and other study personnel (PI, co-investigators, biostatistician and data manager) will be blind to treatment arm allocation. Blinding participants and study personnel is possible because the placebo and active capsules are indistinguishable. Although AEs associated with the active drug may threaten the blind, they are less likely to occur given that participants will all have taken NSAIDs regularly for at least 3 months prior to study onset and the study drug for 2 weeks during the run-in period. We will test the success of blinding by asking subjects and the project coordinator to guess group assignment (allowing for a “don’t know” option) at the end of Phase 1 [73]. We will also ascertain confidence (How confident are you that your guess is correct?) using a 5-point Likert scale ranging from 1 = Not confident at all to 5 = Extremely confident.

D.9 Expected Participant Flow: Our target sample size is 434 subjects (see sample size calculations in D.19). We will randomize 544 subjects to account for a possible 20% loss to follow-up. We will enroll *680* subjects into the run-in period, to allow for a loss of up to 20% during the run-in period [64]. This estimate is conservative, because many of the subjects will already be taking meloxicam and all have been able to tolerate NSAIDs for at least 3 months. Randomization of 15 subjects per month over both sites will enable us to reach our target sample size over 37 months. Subject disposition will be reported in agreement with CONSORT guidelines [74]. The flow chart is included in Appendix 1. Reasons will be recorded to explain ineligibility and all dropouts.

D.10 Data Collection Overview: Data will be collected using standardized questionnaires and forms. The project coordinator will be trained to administer specific instruments during the start-up period. Demographic and clinical characteristics, current medications, social support and expectations will be assessed at baseline. Knee pain severity will be collected at baseline and then weekly. Adherence to study drug, use of acetaminophen and other co-therapies, AEs and goal attainment will be collected weekly. Lower extremity disability, subjects’ global impression of change, and the Health Utility Index Mark 3 (HUI3) (see D.20.a) will be collected at baseline and then at the end of phase 2 (see Table 4). Outcome data will be collected by the project coordinator before each CBT session.

Table 4. Summary of Data to be Collected

Variable	Start of Run-In	End of Run-In	Baseline (Phase 1)	Weekly	End of Phase 2
Demographic	X				
Clinical characteristics	X				
Current medications	X				
Social support	X				
Expectations*			X		
Pain severity	X		X	X	X
Lower extremity disability	X		X		X

Intermittent vs Constant Pain (ICOAP)			X	X	X
Impression of change		X			X
Adverse events		X		X	X
Adherence to study drug		X		X	X
Use of acetaminophen		X		X	X
Use of co-therapies		X		X	X
Goal attainment*				X	X
HUI3 (See D.24)			X		X

D.11 Subject Characteristics: The following independent variables will be collected at baseline to help readers judge the generalizability of the results and to check comparability of the study groups at baseline.

Sociodemographic characteristics: Age, gender, ethnicity, maximum level of education attained, employment status, and living arrangements (living with a spouse, another person, or alone) will be obtained by self-report.

Clinical characteristics: Overall health status and co-morbidity will be ascertained using the Arthritis Impact Measurement Scales [75]. Body mass index will be obtained from the most recent EMR entry. Baseline knee pain and disability will be measured using the WOMAC (detailed in D.12). Psychiatric co-morbidities will be ascertained by chart review.

Current medications: Current medications will be obtained from the chart during the screening chart review and subsequently reconciled with each subject during the baseline interview. In case of discrepancies, the subject's report will be used. Duration of NSAID use (for knee pain) will also be recorded. We will specifically inquire as to Rx and OTC medications, neutraceuticals and supplements.

Social support: Social support will be measured using the 5-item Modified Social Support Survey. Psychometric properties of this instrument include the following: Cronbach's alpha = 0.88, correlates highly with a measure of loneliness and companionship (convergent validity) and poorly with visual impairment (discriminant validity) [76].

Expectations: Subjects' expectations related to the benefits associated with NSAIDs will be assessed at baseline using a 5-point scale ranging from 1 = Not at all effective to 5 = Extremely effective. This measure will be repeated* to assess expectations related to CBT prior to the first session for subjects randomized to the CBT arm during Phase 2.

D.12 Outcome Variables

D.12.a Primary Outcome: The primary endpoint will be between-group differences in the WOMAC pain score measured at 4 weeks. The WOMAC is a disease-specific health status questionnaire. Of the instruments used to assess change in persons with knee OA, the WOMAC has been the most extensively validated and is recommended for (by the Osteoarthritis Research Society) and widely used in OA trials [77,78].

The WOMAC pain scale consists of 5 questions that ask about pain during walking, stair use, lying in bed at night, sitting, and standing. Each question is scored on a 5-point scale, where 0 = None, 1 = Mild pain, 2 = Moderate pain, 3 = Severe pain, and 4 = Very severe pain. Total pain scores range from 0 to 20 with higher scores reflecting worse pain. The WOMAC also includes a lower extremity disability scale. Both the pain scale and disability scale (17 items) can be analyzed separately.

Psychometric properties of the WOMAC scale include good internal consistency with Cronbach's alpha for the pain and disability scales = 0.81 and 0.91, respectively [79]. The intraclass correlation coefficient for pain = 0.95 and for physical function = 0.92 [80]. Validation studies have shown high correlations with other indices probing the same dimensions [77,81]. Rasch analysis suggests that the pain and function scales are unidimensional and are appropriate measures for lower extremity function in patients with chronic arthritis [82]. The WOMAC has generally been found to be more sensitive to change when compared to other measures of functional status in OA including the Health Assessment Questionnaire, the Arthritis Impact Measurement Scales, the Doyle Index,

the Lequesne Index, timed walk and range of motion (relative efficiency compared to other instruments ≥ 1) [77,83]. Though the WOMAC is available using both visual analogue and Likert (WOMAC LK 3.1) scales, in this proposal we will use the latter because it has been validated for use over the telephone [84].

D.12.b Secondary Outcomes

Area under the curve (AUC) of the WOMAC pain scale score over the observation period: AUC will be measured in order to capture the variability in pain that is characteristic of knee OA [85,86]. The AUC is a commonly used measure that combines multiple measurements over a specific time interval into a single index [87]. The AUC_G provides a single score that quantifies each participant's total WOMAC score across the repeated measurements. The formula is given as:

$$AUC_G = \sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i) \cdot t_i}{2}$$

Where m_i denotes the measure at each time and t_i denotes the time between measures. Because measures are collected weekly, t_i is a constant and can be dropped from the equation. The AUC_G is valid regardless of increases or decreases in reported pain over time.

Intermittent vs.Constant Pain: Measure of Intermittent and Constant Osteoarthritis Pain (http://www.oarsi.org/index2.cfm?section=OARSI_Initiatives&content=Pain_Radiological_Indexes) will be used to evaluate the subject's pain experience, including pain intensity, frequency, as well as impact on mood, sleep, and quality of life. This 11-item scale asks subjects to rate their "constant knee pain" and their "knee pain that comes and goes" over the past week. Each item is scored on a scale from 0 to 4, with higher scores indicating a worse pain experience. The ICOAP complements the WOMAC given that the latter focuses on the impact of pain on physical functioning.

Lower extremity disability: Lower extremity functional outcomes will be measured using the WOMAC disability scale (detailed in D.13.a). The physical disability scale contains 17 items that assess the amount of difficulty subjects say they have with climbing stairs, rising from a chair, walking, and other activities of daily living. Responses are measured and scored in the same way as the pain scale.

Global impression of change: To assess global improvement, we will use the Patient Global Impression of Change Scale, a balanced 7-point scale (1 = Much better to 5 = Much worse) asking subjects to rate their change (if any) in pain since starting the study [88]. This item has been well-validated and is recommended as a core outcome measure by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials [89].

Adherence to study medication and use of co-therapies: It is difficult to measure adherence and use of co-therapies in a clinical trial. This is especially true in this study where contact is made by telephone only and many of the medications used are available OTC. We will ask patients to fill in daily medication diaries to record whether or not they took the study drug, the names of any additional co-therapies used (RX and/or OTC), and the occurrence of any AEs. Co-therapies include: analgesics (RX and/or OTC), supplements, and/or topical agents taken for arthritis pain. Eligible subjects will be instructed on how to fill in the diaries after they have agreed to participate. The diaries are meant to be used as reminders/cues during follow-up telephone calls. The project coordinator will ask subjects to refer to their diaries and will ascertain use of medications using the following questions:

- Over the past week, how many days did you use the study drug for your knee pain?
- Over the past week, how many days did you use Tylenol or acetaminophen for your knee pain?
- Over the past week, how many days did you use other medications that were prescribed by one of your doctors for your knee pain?
- Over the past week, how many days did you use other medications, creams or supplements that you got without a prescription for your knee pain?
- Over the past week, how many days did you use any medications for a different problem or type of pain (e.g. headache)?

We intentionally framed the questions so as to facilitate reporting difficulties with adherence or use of non-permitted co-therapies. Although diaries are frequently used as a measure of adherence, the research team felt that asking subjects to mail back diaries each week would be overly burdensome and potentially result in greater amounts of missing data.

Adverse events: AEs are generally collected using either an open-ended approach or a list of close-ended questions. A recent systematic review concluded that there have been too few studies to strongly recommend either one [90]. We will use an open-ended approach to collect AEs. The project coordinator will ask subjects whether they have experienced any AEs (over the past week) on a weekly basis. We will also specifically inquire whether subjects have had interim medical visits, procedures, doctor visits, emergency room or urgent care visits, and hospitalizations. Positive responses to any of these events will lead to focused chart reviews. AEs are further described in Section D.16.

D.13 Moderating Variable

Goal attainment: For those randomized to CBT, the extent to which each specified intersession goal is met will be measured each week using a numeric rating scale ranging from 0 = Did not work at all on goal(s) to 10 = Completed goal(s).

D.14 Retention: Subjects will be paid $25 after the baseline interview and $25 after the 4- and 10-week follow-up assessments. These incentives are consistent with amounts paid to subjects for other similar studies at our institution.This trial will also benefit from the expertise of the CBT therapists and the relationships they will establish with each subject. The experience of the PRIME Center's personnel and the relationships they engender with study subjects is a major factor underlying the success of the trials conducted at our center.

D.15 Treatment Fidelity: To enhance CBT treatment fidelity we will 1) use treatment manuals and patient handouts that have been developed and previously used at our center; 2) hire CBT therapists who have received training in the manualized CBT treatment protocol; 3) include individualized goals to motivate subjects; and 4) identify barriers towards skill practicing and goal attainment each week. To measure treatment fidelity, we will measure goal attainment weekly (see D.12). In addition, we will audiotape, to the extent possible, all treatment sessions using a digital phone recording system (Sparky+ USB Phone Call Recorder, V3) that records both sides of the telephone conversation. The phone recorder connects the phone to the computer such that phone calls can be recorded automatically or manually. Calls are saved directly to the VA-approved server and can be accessed using a username and password for security. Explicit consent will be obtained from subjects to audiotape these conversations. In our previous experience less than 2% of subjects refused to be audiotaped during CBT sessions.

Dr. Heapy and the psychology technicians will listen to a random 10% of the other therapist's CBT sessions to ensure adherence to the treatment manual. Adherence will be measured using a modified version of the Yale Adherence and Competence System-Second Edition (YACS-II) [91]. This scale allows for the systematic evaluation of therapist adherence to pre-specified elements of the treatment such as rationale for, and explanation of each coping skill, setting of skill practice goals, encouragement of self-monitoring, rapport building and adherence to session time limits. Drs. Heapy and the psychology technicians will meet weekly to review the rated sessions, note and reinforce successful adherence to the manual and provide corrective feedback to the therapist if and when treatment drift occurs.

D.16 Safety

D.16.a Notification of Patients and Providers: Patients will receive information about the risks of NSAIDs during the consent process. All providers in the VACHS and Providence VA Medical Center will be notified about the research project by email and the PI will describe the study at the monthly primary care provider team meeting for each firm, prior to study onset and every 6 months thereafter. In addition, we will notify the primary care provider and relevant specialists each time a subject is enrolled to ensure that they are aware of and understand the study protocol. We will also send an email alert to physicians should we find that their patients have contraindications to NSAID use or are taking a high risk combination of antiplatelet and/or anticoagulant medications. We will also notify providers of AEs developing in their patients during the study.

D.16.b Adverse Event Monitoring: CBT is not associated with any expected AEs apart from the inconvenience associated with participating in the telephone sessions and practicing the required skills. Few

NSAID-related AEs are expected because all participants had to have tolerated NSAIDs during the run-in period and for at least 3 months prior to enrollment in order to be eligible to participate. Still, subjects remain at risk for NSAID-induced toxicity. Subjects will be asked whether or not they developed any AEs during the prior week. All AEs will be reported to the PI as they are discovered. EMR data will be reviewed for all subjects having outpatient appointments or hospitalizations during the study period. Development of a severe or life-threatening AE will result in study drug discontinuation. However, all subjects will continue to be followed until the end of the study period. All unexpected and serious AEs will also be reported to the VA Central IRB and the Data Safety Monitoring Board (DSMB) within 24 hours. In addition, a local Study Specific AE Committee made up of 2 physicians who are not on the project team will review a cumulative report of unexpected and moderate to severe AEs every 4 weeks (or more often if necessary). The Committee will confirm or modify the PI's assessment in order to ensure that no concerning patterns of AEs emerge.

D.16.c Suicide Ideation: If a research team member learns of suicidal ideation with a subject during a telephone session, the team member may ask three additional questions to gather important information to provide for the VA Suicide Hotline so that they can assess if the subject is in imminent danger. If suicidal ideation is expressed, the following three questions may be asked:

1. Have you ever tried to kill yourself?
2. Do you have any specific plans to kill yourself now?
3. Do you have the means to carry out those plans?

If the team member is able to immediately determine that the subject is an imminent threat, then the "warm transfer" (established guidelines between VA National Suicide Prevention Hotline and CSRDS) will be by-passed and local law enforcement authorities will be contacted to alert them of the imminent threat and to ask for assistance escorting the subject to a mental health provider, emergency room, urgent care, etc. Otherwise, the subject will undergo the "warm transfer" as needed. These individuals will be dropped from the study.

D.16.d Adverse Event Classification and Grading: We will classify AEs by organ system (gastrointestinal, renal, hepatic, cardiovascular, other) [52]. AEs will be further classified by whether or not they required treatment and/or hospitalization. We will use the Naranjo algorithm to estimate the probability that the study drug caused the AE [92]. Two physicians (LF and LS) will independently score each AE using the Adverse Drug Reaction probability scale [92]. This validated scale includes 10 items coded as Yes, No or Do not know. A scoring algorithm generates a total score with a possible range of -4 to +13. AEs with scores of ≥ 9 are classified as definite; 5-8 as probable; 1-4 as possible, and < 1 as doubtful. The scale has been shown to have high within and inter-rater reliability (r = 0.91-0.98 and r = 0.84 to 0.93 respectively) [92]. Disagreements will be adjudicated by a third VA physician (Dr. Avlin Imaeda; Section of Gastroenterology, VA CT - see letter of support). The PI will grade each AE for severity using the Rheumatology Common Toxicity Criteria v.2.0 listed in Table 5 [93]:

Table 5. Adverse Event Severity

Category	Definition
Mild	Asymptomatic, short duration (< 1 week), no change in lifestyle, no Rx required
Moderate	Symptomatic, duration 1-2 weeks, occasionally alters lifestyle, Rx provides relief
Severe	Prolonged symptoms, major functional impairment, hospitalization < 24 hrs
Life threatening	At risk of death or substantial disability, especially if permanent, hospitalization > 24 hrs

D.17 Sample Size Calculations: The primary endpoint is the difference in mean pain scores between the NSAID and placebo groups (as measured by the WOMAC pain subscale) at 4 weeks. The sample size was calculated using NCSS/PASS 2008 Power Analysis of a Non-Inferiority Test of The Difference of 2 Means: Numeric Results for Non-Inferiority Test (H0: D >= |E|; H1: D < |E|); where |E| is the magnitude of the margin of equivalence. D is the mean difference at which the power is computed. D = Mean1 - Mean2.

The range of the WOMAC pain subscale is 0-20 and the minimum clinically important difference (MCID) is 2.1 [72,94]. We set the equivalence margin to 1.0 which is less than 50% of the MCID. A sample size of 434 (217 per arm) achieves 90% power to detect non-inferiority using a 1-sided, 2-sample t-test. A 1-sided test is

recommended for non-inferiority trials. The true difference between the means is assumed to be 0.00. The significance level (alpha) of the test is conservatively set at 0.025. The data are drawn from populations with standard deviations of 3.20 [83].

We will enroll 680 subjects in the 2-week run-in period to account for a possible 20% loss. We will randomize 544 subjects to enable a further 20% loss over the 4-week withdrawal period. The use of a run-in period and a RWT design both tend to decrease the required samples size; therefore these estimates are conservative.

Assuming a further 25% loss in Phase 2, we will have 80% power to detect non-inferiority under the same assumptions.

Stopping Rules/Removal from Study:

If patient reports use of another NSAID beside meloxicam and, despite being asked to stop, is unable to do so over the subsequent week, he will be removed from the study.

If patient reports taking more than the maximum dose of 3g of Tylenol daily, and, despite being asked to limit the dosage is unable to do so over the subsequent week, he will be removed from the study.

We will not include stopping rules due to pain, because:

1) All subjects are receiving therapy for knee pain.

2) Stopping rules are not typically included in RCTs for knee OA, including withdrawal trials.

3) Analgesic use will be recorded and accounted for in the analyses.

Patients reporting an escalation of pain will only be removed from the study if they are unable to comply with the study regulations and the stopping rules stated above.

D.18 Analyses of Aims 1 and 2

D.18.a Phase 1 Analyses

Hypothesis 1: Subjects randomized to placebo will not experience more knee pain than subjects randomized to continue NSAIDs at 4 weeks.

All analyses will be performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC). *The SAS t-test procedure* will be used to calculate the means and standard deviations of each group, and the 95% CI of the difference. Both intention-to-treat (ITT) and per-protocol (PP) analyses will be conducted, and compared. The model will be adjusted for study site and the treatment covariates will be represented by indicator variables. We will utilize multiple imputation methods to account for missing WOMAC scores, and compare the results of imputed models to both ITT and PP analyses [95,96]. Multiple imputation is a Monte Carlo technique in which the missing values are replaced by m>1 simulated versions. In Rubin's method for “repeated imputation” inference [95], each of the simulated complete datasets is analyzed by standard methods, and the results are combined to produce estimates and confidence intervals that incorporate missing-data uncertainty.

The adequacy of the randomization will be assessed by comparing baseline demographic and clinical characteristics between the 2 treatment groups. Variables will be summarized (means, proportions, etc.) and continuous variables will be compared using 2-sample t-tests, while differences in categorical variables will be examined using chi-square tests. Characteristics found to be significantly different between conditions will be included as covariates in subsequent analyses to determine if they alter the conclusions of the study. The success of blinding will be compared across groups using chi-square tests and 2-sample t-tests for the proportion guessing correctly and confidence ratings, respectively.

Hypothesis 2: The AUC score in the placebo arm will not differ from the AUC in the continued NSAID arm at 4 weeks.

The SAS MEANS procedure will be used to calculate the means and standard deviations of each group AUC score, and the 95% CI of the difference. Both intention-to-treat (ITT) and per-protocol (PP) analyses will be conducted and compared.

D.18.b Phase 2 Analyses

Hypothesis 3: Subjects participating in the CBT program will not experience more knee pain than subjects continuing NSAIDs at 16 weeks.

The SAS t-test procedure will be used to calculate the means and standard deviations of each group and the 95% CI of the difference as described in Hypothesis 1.

Hypothesis 4: The AUC score in the CBT arm will not differ from the AUC in the continued NSAID arm at 16 weeks.

The SAS MEANS procedure will be used to calculate the means and standard deviations of each group AUC score, and the 95% CI of the difference as described in Hypothesis 2.

Hypothesis 5: Subjects participating in the CBT program will not report greater overall worsening (global change) or levels of lower extremity disability compared to subjects randomized to continued NSAID use.

We will use linear mixed effects (LME) models to examine differences in the slope of global change and disability by group over time. LME models account for the clustering induced by repeated measures on individual patients and includes both between-groups and within-subject effects, allows for missing data, and measurements at different time intervals. Data from different subjects are assumed to be independent, while the correlation structure of the repeated measurements within subjects is modeled via parameterization of the covariance structure. Analyses will be performed using SAS PROC MIXED. Dichotomized variables will be analyzed using generalized estimating equations.

***Hypothesis 6: Subjects participating in the CBT program will not report greater use of co-therapies compared to subjects randomized to continued NSAID use*.**

Group differences in the number of days using co-therapies per week, a count variable, will be modeled using Poisson regression analysis [97]. We will correct for overdispersion - a common problem in Poisson models that occurs when the variance of the count dependent variable is greater than the mean - by setting the scale parameter to the deviance divided by the residual degrees of freedom. Incidence rate ratios representing the risk of co-therapy use will be obtained from model results by exponentiating the parameter estimates. We will also examine the moderating effect of goal attainment on co-therapy use.

Hypothesis 7: Goal attainment will be associated with improved primary and secondary outcomes.

We will use latent class regression analysis to model the longitudinal trajectory of the 0-10 weekly ratings of coping skill acquisition on subsequent pain, disability, global change and co-therapy use at 3 months [98]. These models allow for the regression parameters to differ across the unobserved (latent) groups trajectories, and are performed in a single model. LME models and multiple imputation methods will be used to model missing outcome data because they have been shown to be superior to other methods, such as last observation carried forward, in the analysis of repeated measures data [74,99].

Aim 3: To estimate the potential cost-effectiveness of CBT compared with continued NSAID use.

D.19 Healthcare Utilization: Subjects' OA-related healthcare utilization will be measured using VA Regional Data Warehouse (RDW) data for all OA-related outpatient visits (emergency room, primary care, urgent care, rheumatology, orthopedic surgery, physical therapy, and pain management clinics) over 12 months prior to the run-in period and 6 to 12 months following randomization, depending upon enrollment rates, to allow more stable estimates of pre-, during, and post-study utilization and the persistence of any intervention effects over time. RDW data will also be used to identify the total number of consults placed to the Bone and Joint Clinic (both orthopedic and rheumatology referrals), *Physiatrists*, pain management and physical therapy for all study subjects. Within-group differences in total number of OA-related outpatient, urgent care and emergency room visits and consults for both treatment arms will be evaluated using paired t-tests. Between-group differences in the change in total OA-related outpatient, urgent care and emergency room visits and consults over the 14-week study period will be evaluated using unpaired t-tests.

D.20 Cost-Effectiveness: To evaluate the short- and long-term health and economic benefits of discontinuing NSAIDs and then starting CBT, we will compare OA-related VA health services utilization, total direct medical costs, and the incremental cost-effectiveness ratio (in US dollars per quality-adjusted life-year) associated with continued NSAID use versus CBT at 14 weeks, 1 and 10 years.

D.20.a 14-Week Cost-Effectiveness: To estimate cost-effectiveness of the placebo followed by CBT arm compared to continued NSAID use over the 2-phase trial, we will calculate the incremental cost-effectiveness ratio (ICER), reported in 2011 US dollars per quality-adjusted life-year (QALY) gained, for each treatment arm, including the withdrawal period. QALYs will be estimated using the HUI3. The HUI3 is a generic, preference-weighted health status instrument that evaluates 8 attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain/discomfort), each coded using 5 or 6 levels reflecting increasing severity or disability. The HUI3 is a widely used, valid, responsive, and efficient measure of health in OA as well as many other chronic conditions [100-102]. We chose this measure over the shorter EQ-5D because its ceiling effects are lower [102]. As the HUI3 assesses the prior 4 weeks of symptoms, we will collect the HUI3 at baseline and then monthly in order to provide a complete AUC for quality of life estimation during the study period. Costs will be estimated from the VA's perspective. Costs will consist of treatment-specific costs, OA-related health services utilization costs and costs associated with AEs. All cost data will be obtained from the VA Decision Support System National Data Extracts. For the NSAID arm (referent), treatment costs will consist of outpatient pharmacy costs derived from VA pharmacy cost data combined with the mean daily pill usage of individuals in the active treatment arm during the 4-week RWT. We will value productivity losses through the use of QALYs, rather than monetarily, per the Panel on Cost-Effectiveness Analysis of the U.S. Public Service's recommendations [103].

D.20.b 1- and 10-Year Cost-Effectiveness: To extrapolate the longer-term economic value of CBT, we will estimate 1- and 10-year ICERs using a state transition Markov model and use sensitivity analyses to explore the effect of varying levels of efficacy persistence. The purpose of the sensitivity analyses is to identify upper and lowers bounds regarding the uncertainty of long-term CBT efficacy. We will accomplish this by running the model assuming varying costs, efficacy and adverse event rates for both treatment arms.

Although there is a paucity of evidence on the long-term persistence of CBT in providing relief for knee OA, studies have demonstrated therapeutic persistence following treatment discontinuation for similar interventions ranging from 6 months in knee OA [9] to 12 months in low back pain [105], but complete loss of therapeutic effect after 6 years following treatment for depression [106]. We will therefore examine scenarios in the 1-year analysis that explore the impact of how quickly (if at all) CBT efficacy wanes without additional interventions (Table 6). In addition, we will explore the cost-effectiveness of repeating an abbreviated CBT program (10 weeks) at varying intervals to allow extrapolation to 10 years (Table 6). We will examine 3 separate extended cost assumptions (lowest, average and highest cost accrued over study period extrapolated over 1 and 10 years). We will assume a range of long-term efficacy and AEs associated with NSAIDs drawn from the published literature. We will calculate 1 and 10 year ICERs for CBT compared to continued NSAIDs for each combination of cost, CBT and NSAID assumptions. Continued CBT costs will include the cost of a full time therapist and 20% percent effort of an administrator to process referrals. In order to calculate the 1- and 10-year ICERs, utilities and costs will be annualized following the above assumptions.

Table 6. CBT Efficacy Assumptions for Sensitivity Analyses

1-Year	10-Year
Stable over period	Stable over period
Decreases to no effect over 9 months	Decreases to no effect over 1 year
Decreases to no effect over 6 months	Decreases to no effect over 2 years
Decreases to no effect over 3 months	Decreases to no effect over 5 years
Decreases to no effect over 1 month	Decreases to no effect over 10 years

D.20.c Model: The Markov model will be comprised of 19 health states representing 9 strata of knee pain and functional status (defined by tertiles of WOMAC pain scale and lower extremity disability scale scores, respectively), presence or absence of severe treatment-related AEs (e.g., gastrointestinal bleed or renal failure requiring hospitalization) and death. The cycle length will be 10 weeks. QALYs will be derived from study data and supplemented with published literature. The impact of mild AEs on QALYs will be averaged over all health states for a given treatment strategy, but will not incur additional costs.

We will use TreeAge, a simulation software package that combines decision analysis and state transition or Markov processes with detailed outputs containing all internal calculations for model debugging and internal validation. We will run the model as a Monte Carlo simulation, where each hypothetical patient proceeds through varying clinical stages of disease or events [107]. This type of simulation is probabilistic: the modeler defines the overall probability of a particular event occurring, but does not know ahead of time whether a particular event will happen to a particular simulated patient (unless specified probability is exactly "1" or "0"). Monte Carlo simulation provides several advantages. First, the model produces a distribution of results for the outcome of interest, more accurately representing the heterogeneity observed in real populations. Second, it is possible to run the model to reflect areas of uncertainty without altering the model structure, which is valuable when data on probability estimates are limited. We will employ a systematic validation approach [103] including one-way analyses of variables over plausible ranges using numeric and graphic assessment of results [108]. We will also examine extreme scenarios where the outcome is clinically obvious. The model will estimate 1- and 10-year costs and QALYs associated with placebo followed by CBT versus continued NSAID use under the assumptions described above, and allow calculation of the 1- and 10-year ICERs. Costs and QALYs will be discounted at 3% per year.

Hypothesis 8: Discontinuing NSAIDs and initiating CBT will result in a greater overall reduction in VA health services utilization compared to continued NSAID use.

Documented reductions in health care utilization among participants during the study may be due either to greater clinical effect of CBT versus NSAIDs, or alternatively, to an effect of study participation independent of treatment effect. We will quantify the impact of potential protocol-induced reductions in health care utilization on cost-effectiveness by performing sensitivity analyses alternatively assuming: 1) no change in utilization in either treatment group, 2) equal reductions in both groups, and 3) greater reductions in the CBT versus continued NSAID group. We will also define utilization thresholds at which the favored strategy (CBT versus continued NSAID) changes.

Hypothesis 9: Discontinuing NSAIDs and initiating CBT will offer cost savings compared to continued NSAID use when considered over a 10-year time period.

Again, using sensitivity analyses noted above, we will explore the impact of varying long-term assumptions on cost-effectiveness, thereby providing thresholds for CBT efficacy, health care utilization and NSAID toxicity at which the favored strategy changes**.**

D.21 Data Management: Data management will be led by Dr. Cynthia Brandt, Director of the Prime Center's Informatics Core. Dr. Brandt has extensive experience in study design, preparation of study forms, and management of data and preparation of reports. Dr. Brandt, along with the data manager, will develop a Data Management Operations Manual during the study start-up period to describe the computing environment, data entry and data management procedures. She will oversee interim monitoring to track enrollment, protocol adherence, completeness of data collection, safety, and adherence. This monitoring will be performed by the project/data manager (blinded to treatment assignment). Aggregate results (both groups combined) will be reported on a weekly basis to the PI. Results by group (without group labels) will be reported every 6 months to the DSMB.

D.21.a Clinical Study Data Management System: We will use RedCap, a software application that supports computerized interviews, batch data entry, and basic project administration. Using this existing flexible database will substantially reduce time required for the database development and data management. Survey data will be entered into electronic forms. Data reports and SAS extracts for statistical analysis will be made available on the VA server to authorized researchers

D.21.b Quality Assurance and Control: We will hold biweekly progress reports with all research personnel to monitor enrollment, adherence to the study protocol and AEs. Personnel will be trained to enter data into RedCap. All data entry will be 100 percent verified by someone other than the original keyer. Any discrepancies will be flagged and resolved with the project manager. RedCap will be used to generate a number of reports as well as reminders to help monitor and manage the data collection process to ensure completeness of evaluation. RedCap has a built in mechanism to ensure that duplicate IDs and forms are not entered. Reports will be run by the data manager to look for outstanding forms for participants that are due for entry and to monitor protocol compliance. RedCap stores audit trails of errors detected and corrected as well

as all data changes. Records that have completed the defined cycle of entry, verification, and editing are considered “clean” and can be “locked”. Logic checks and range limits are built into the forms and will be used to facilitate quality data at the time of entry. Enrollment, survey completion and data entry quality and timeliness of entry will be monitored weekly with reports. The data manager will check for data inconsistencies, omissions, and errors regularly. Data questions or problems will trigger data queries and analyses of missing data will be done periodically to ensure that all forms are entered and available for analysis. RedCap maintains an electronic audit trail of all modifications to a study’s data, including the user who made the change, the date and time, and each data item changed and its previous value and new value. Several levels of backup of the database will be performed on a regular basis, including full backup daily and incremental backup during the day.

D.23.c Data Security: All data will be handled in accordance with VA Office of Research and Development regulations. Several layers of security will be employed to protect study data, such as: a) login procedures with usernames and passwords for access to the data, b) storage of data on the VA SQL Server, and c) disaster recovery procedures with redundant data storage and backup. RedCap implements a variety of other security features at several different levels, including “role-based” user privileges. The person in charge of the study can specify, for example, that a particular person is allowed 1) “read only” access to that study’s data, 2) “read/edit” access, 3) the ability to see only certain case report forms, and/or 4) the ability to run reports or export data for analysis. All data will be kept in a unique study file with a unique study identification number. The study files containing these data will not contain any identifying information. A separate file will link study identification numbers with participants’ names and telephone numbers. All study staff will receive HIPAA training and Human Subjects Protection training. Users will certify that they are HIPAA trained and will act in full compliance of HIPAA regulations.

E. POTENTIAL PITFALLS AND SOLUTIONS

The number of Veterans with OA on NSAIDS in the VACHS and Providence VA Medical Center indicates that we should not have any difficulty reaching our target sample size. Nonetheless, we acknowledge that it is always difficult to recruit for a clinical trial. Therefore, we will track enrollment carefully, and should we fail to meet predefined enrollment goals, we will expand to include other VA Medical Centers within VISN1. Expanding the number of sites is feasible because all procedures and data are collected by telephone. Because the study design does not include in-person assessments, we are not able to obtain “objective” measures of disease activity or performance. Unlike rheumatoid arthritis, we would not expect any changes in physical examination or laboratory findings in the majority of subjects over the course of the proposed study. However, lower extremity performance measures (e.g. timed walk or sit-to-stand tests) can add valuable information in OA clinical trials. After extensive discussion with the research team and other experts in OA, it was decided that asking subjects to come to the VA to perform a battery of lower extremity function tests was not warranted given that our primary objective was to address the needs of Veterans having limited access to VA services, all other aspects of the study are conducted by telephone, and lower extremity function will be partially assessed using a well-validated self-report measure. We will use diaries to help subjects keep track of medication use (study drug and co-therapies), but will not use the diaries as an outcome measure because having subjects mail them back would be burdensome and risk leading to substantial missing data. Given that a RWT for NSAIDs has not yet been done, we felt that it was important to demonstrate short-term efficacy first; thus long-term effectiveness will not be evaluated.

F. DISSEMINATION PLAN

The results of this study will be relevant to patients, providers who care for patients with knee OA, implementation and health services researchers, and policy makers who are responsible for developing and implementing pain initiatives within the VHA. Dissemination activities will include presenting study results to patients at patient education events, and to researchers at local and national conferences. Additional presentations to healthcare providers will occur at the VA Rheumatology Consortium annual meetings and in relevant seminars and CME programs. All presentations will include development and dissemination of project-related issue briefs, slide presentation sets, and printed materials. An additional strategy for dissemination of findings will be via the preparation and distribution of summary reports. The Coordinating Committee will advise and coordinate next steps for dissemination, including dissemination to other relevant entities such as Pain Management Coordination teams and committees and the Pain Management Education, Guidelines,

Outcomes and Performance Measures Working Groups. We will also post a summary of the study findings and implications on the Pain Management Committee's website in a format appropriate for VA patients. We will call on the expertise of the National Pain Research Working Group to assist in dissemination of the results of this study. Over 80 VA and non-VA pain-relevant investigators form this network that serves multiple goals including identification of priorities for pain research, advocacy to promote increased funding for pain-relevant research, development of collaborative research projects, and communication and dissemination of research findings. Among several specific projects, this group has published special issues of 3 journals on pain and pain management that highlight pain research in the VHA. Face-to-face meetings of the group occur on an annual basis and further foster communication and collaboration in conjunction with the National HSR&D meeting.

Finally, in collaboration with the Center for Information Dissemination and Educational Research, information from this project will be disseminated via cyber seminars, a state-of-the-art, web-based conferencing technology that enables dynamic interaction among presenters and seminar participants from one's desktop. In addition, archived versions of seminars are available on the web for viewing on demand. Dissemination efforts will be facilitated by the team's close collaboration and association with the VA Rheumatology Consortium and the VHA National Pain Management Strategy Coordinating Committee. This committee, chaired by study Co-Investigator Dr. Robert Kerns, was established in 1998 to oversee the development and implementation of the VHA National Pain Management Strategy. The committee meets monthly, providing leadership, coordination, facilitation and oversight of the VA National Pain Management Strategy. Our close collaboration with this committee through Dr. Kerns will not only help ensure that the study produces findings that are quickly actionable, but will also provide a national infrastructure for rapid dissemination.

The dissemination of telephone-based CBT will be facilitated by an initiative undertaken by the Office of Mental Health Services to train VA mental health providers in evidence-based psychotherapies. The Evidence-Based Psychotherapy (EBP) initiative, includes a national training program that provides in-person training workshops in evidence-based psychotherapies followed by weekly expert supervision of an actual therapy case for 6 months. The EBP initiative has already rolled out several evidence based therapies for post-traumatic stress disorder and depression. The national rollout of training in CBT for chronic pain will occur over the next 2.5 years. Dr. John McKellar, Training Coordinator of CBT for Chronic Pain Management, estimates that approximately 560-640 mental health providers will complete the training over the course of the rollout. Thus, the expertise to deliver CBT for chronic pain will be increasingly available within VA through this ongoing initiative without the need for further investment of resources.

G. HUMAN SUBJECTS: Details related to the inclusion of human subjects are included as a separate attachment.

H. WOMEN AND MINORITIES: At VACHS, approximately 85% of Veterans are White, 14% are Black, 0.3% are Pacific Islanders, 0.2% are Native American, and 0.1% are Asian. We will oversample women and Black Veterans in order to represent these demographic groups as best as possible. The CT and RI VA medical centers serve overlapping geographic regions and the demographic characteristics are comparable across both sites. There are approximately 2,000 women enrolled in the VACHS and just over 1,000 in the Providence VA Medical Center.

I. PROJECT MANAGEMENT PLAN

I.1 Plan and Timeline: The project timeline, (see Gantt chart, Appendix 3), indicates that in the first quarter of year one, we will hire and train a project coordinator and 2 psychology technicians. During the study start-up period we will make minor modifications to the CBT manual and patient handout, develop the manual of operating procedures, the data entry forms and the subject tracking system. Towards the end of the first quarter we will notify/educate providers about the study and its procedures. Biweekly research progress meetings with the PI, CBT therapists, project coordinator and data manager will occur throughout the 4 year study period. The DSMB will meet during the study start-up period to review study protocols and every 6 months once enrollment begins. Subjects will be enrolled over 37.5 months and analyses of Aims 1 and 2 will occur in the second and third quarters of the fourth year. Cost data will be collected starting in Year 2. The Markov model will be constructed and debugged in Years 2 and 3 and analyses of the cost data will occur in Year 4. Concentrated work on manuscript preparation and dissemination will occur in the latter half of Year 4.

I.2 Facilities and Resources: This project will benefit from the resources and facilities of the VACHS PRIME Center, the VACHS Clinical Epidemiologic Center and the Providence VAMC. Please see Facilities and Resources Attachment.

I.3 Specific Roles of the Key Personnel (Further detailed in Budget Justification)

Liana Fraenkel, MD, MPH. Principal Investigator (4.5 cal ms). As the PI, Dr. Fraenkel will have overall responsibility for this project and will oversee all research activities from inception to completion of the project. She will be the primary investigator responsible for interpretation of the analysis and will be responsible for preparing manuscripts, presenting the study results at scientific meetings, and dissemination-related activities.

Cynthia Brandt, MD. Co-Investigator (0.6 cal ms): Data management will be led by Dr. Cynthia Brandt, Director of the Prime Center's Informatics Core. She will directly supervise the data manager and assist in preparation of the electronic study forms and database for the trial.

Joseph Goulet, PhD. Co-Investigator (1.2 cal ms yr 1 and 2.4 cal ms yr 4): Dr. Goulet will be responsible for performing all analyses.

Alicia Heapy, PhD. Co-Investigator (1.2 cal ms): Dr. Heapy will hire the psychology technicians. She will be responsible for ensuring quality control of all aspects related to the CBT protocol and treatment fidelity. Dr. Heapy will meet weekly with Dr. Higgins and the psychology technicians throughout the study to review adherence to the manual.

Francis Keefe, PhD. Consultant: Dr. Keefe is an expert in behavioral approaches to treating chronic pain. He has previously developed a CBT program for OA and will review and help revise the required program for this project.

Robert Kerns, PhD. Co-Investigator (0.6 cal ms): As VHA National Program Director for Pain Management, Dr. Kerns will assist in the development and implementation of a comprehensive plan for dissemination of the findings with a particular focus on their clinical and policy implications.

Doug Leslie, PhD. Consultant: Dr. Leslie is an expert in dealing with VA-related costs and has an established working relationship with the PRIME Center. He will work closely with Dr. Suter to accomplish Specific Aim 3 and will participate in writing abstracts and manuscripts describing utilization of services related to the intervention and the cost-effectiveness of replacing NSAIDs with CBT in the VHA.

Sam Poon, MD. Local Site Principal Investigator (1.2 cal ms): Dr. Poon will assist in recruitment at the Providence VAMC site. He will meet with patients to describe the study and will obtain written consent. He will also contribute to interpreting study results and writing abstracts and manuscripts.

Robert Swift, MD, Ph.D Mentor (1.2 cal ms): Dr. Swift will supervise Dr. Poon's research-related activities and advise him on an as-needed basis. He will also contribute to interpreting study results and writing abstracts and manuscripts.

Lisa Suter, MD. Co-Investigator (0.6 cal ms yr 1 and 1.2 cal ms yrs 2-4): Dr. Suter will perform the cost-effectiveness analysis and lead the abstracts and manuscripts related to these results.

REFERENCES CITED

1. Asch SM, McGlynn EA, Hogan MM, et al. Comparison of quality of care for patients in the Veterans Health Administration and patients in a national sample. Ann Intern Med 2004;141:938-45.
2. Felson DT, Lawrence RC, Hochberg MC, et al. Osteoarthritis: New Insights. Part 2: Treatment approaches. Ann Intern Med 000;133:726-37.
3. Porcheret M, Jordan K, Jinks C, et al. Primary care treatment of knee pain. Rheumatology 2007;46:1694-700.
4. Bjordal JM, Ljunggren AE, Klovning A, Slørdal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain. BMJ 2004;329:1317-20.
5. Scott DL, Berry H, Capell H.The long-term effects of non-steroidal anti-inflammatory drugs in osteoarthritis of the knee. Rheumatology 2000;39:1095-101.
6. Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain. Eur J Pain 2007;11:125-38.
7. Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ. Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. J Clin Sleep Med 2009;15:355-62.
8. Lin EHB. Depression and osteoarthritis. Am J Med 2008;121:S16-S9.
9. Keefe FJ, Caldwell DS, Williams DA, et al. Pain coping skills training in the management of osteoarthritic knee pain: A comparative study. Behavior Therapy 1990;21:49-62.
10. Keefe FJ, Caldwell DS, Williams DA, et al. Pain coping skills training in the management of osteoarthritic knee pain-II: Follow-up results. Behavior Therapy 1990;21:435-47.
11. Kidd B, Langford R, Wodehouse T. Current approaches in the treatment of arthritic pain. Arthritis Res Therapy 2007;9.
12. Jordan KP, Wilkie R, Muller S, Myers H, Nicholls E, et al. Measurement of change in function and disability in osteoarthritis: current approaches and future challenges. Curr Opin Rheumatol 2009;21:525-30.
13. Kazis LE, Miller DR, Clark J, et al. Health-related quality of life in patients served by the Department of Veterans Affairs: Results from the Veterans Health Study. Arch Intern Med 1998;158:626-32.
14. Briggs A, Scott E, Steele K. Impact of osteoarthritis and analgesic treatment on quality of life of an elderly population. Ann Pharmacotherapy 1999;33:1154-59.
15. Kotlarz H, Gunnarsson CL, Fang H, Rizzo JA. Osteoarthritis and absenteeism costs: Evidence from US national survey data. J Occup Environ Med 2010;52:263-8.
16. Dominick KL, Golightly YM, Jackson GL. Arthritis prevalence and symptoms among US non-veterans, veterans, and veterans receiving Department of Veterans Affairs Healthcare. J Rheumatol 2006;33:348-54.
17. Hawker G, Wright J, Coyte P, et al. Health-related quality of life after knee replacement. J Bone Joint Surg Am 1998;80:163-73.
18. Lee C, Straus WL, Balshaw R, Barlas S, Vogel S, Schnitzer TJ. A comparison of the efficacy and safety of nonsteroidal antiinflammatory agents versus acetaminophen in the treatment of osteoarthritis: A meta-analysis. Arthritis Care Res 2004;51:746-54.
19. Jordan KM, Arden NK, Doherty M, et al. EULAR recommendations 2003: An evidence based approach to the management of knee osteoarthritis. Ann Rheum Dis 2003;62:1145-55.
20. Meek IL, van de Laar MAFJ, E. Vonkeman H. Non-steroidal anti-inflammatory drugs: An overview of cardiovascular risks. Pharmaceuticals 2010;3:2146-62.
21. Vonkeman HE, van de Laar MAFJ. Nonsteroidal anti-inflammatory drugs: Adverse effects and their prevention. Semin Arthritis Rheum 2010;39:294-312.
22. Abraham NS, Castillo DL, Hartman C. National mortality following upper gastrointestinal or cardiovascular events in older veterans with recent nonsteroidal anti-inflammatory drug use. Alimentary Pharmacol Ther 2008;28:97-106.
23. Abraham NS, El-Serag HB, Johnson ML, et al. National adherence to evidence-based guidelines for the prescription of nonsteroidal anti-inflammatory drugs. Gastroenterology 2005;129:1171-8.
24. Beck AT, Dozois DJA. Cognitive therapy: Current status and future directions. Ann Rev Med 2011;62.
25. Turk DC, Meichenbaum D, Genest M. Pain and behavioral medicine: A cognitive- behavioral perspective. Guilford Press;1987.
26. Naylor MR, Naud S, Keefe FJ, Helzer JE. Therapeutic interactive voice response to reduce analgesic medication use for chronic pain management. J Pain 2010;11:1410-9.

27. Calfas KJ, Kaplan RM, Ingram RE. One-year evaluation of cognitive-behavioral intervention in osteoarthritis. Arthritis Rheum 1992;5:202-9.
28. Dixon KE, Keefe FJ, Scipio CD, Perri L, Caitlin M, Abernethy AP. Psychological interventions for arthritis pain management in adults: A meta-analysis. Health Psychol 2007;26:241-50.
29. Cronan TA, Groessl E, Kaplan RM. The effects of social support and education interventions on health care costs. Arthritis Care Res 1997;10:99-110.
30. Mazzuca SA, Brandt KD, Katz BP, Hanna MP, Melfi CA. Reduced utilization and cost of primary care clinic visits resulting from self-care education for patients with osteoarthritis of the knee. Arthritis Rheum 1999;42:1267-73.
31. Rene J, Weinberger M, Mazzuca SA, Brandt KD, Katz BP. Reducation of joint pain in patients with knee osteoarthritis who have received monthly telephone calls from lay personnel and whose medical treatment regimens have remained stable. Arthritis Rheum 1992;35:511-15.
32. Maisiak R, Austin J, Heck L. Health outcomes of two telephone interventions for patients with rheumatoid arthritis or osteoarthritis. Arthritis Rheum 1996;39:1391-9.
33. Allen KD, Oddone EZ, Coffman CJ, et al. Telephone-based self-management of osteoarthritis. Ann Intern Med 2010;153:570-9.
34. Lovell K, Cox D, Haddock G, et al. Telephone administered cognitive behaviour therapy for treatment of obsessive compulsive disorder: Randomised controlled non-inferiority trial. BMJ 2006;333:883.
35. Taylor S, Thordarson DS, Spring T, et al. Telephone-administered cognitive behavior therapy for obsessive-compulsive disorder. Cognitive Behav Ther 2003;32:13-25.
36. Mohr D, Hart S, Marmar C. Telephone administered cognitive-behavioral therapy for the treatment of depression in a rural primary care clinic. Cognitive Ther Res 2006;30:29-37.
37. DuHamel KN, Mosher CE, Winkel G, et al. Randomized clinical trial of telephone-administered cognitive-behavioral therapy to reduce post-traumatic stress disorder and distress symptoms after hematopoietic stem-cell transplantation. J Clin Oncol 2010;28:3754-61.
38. Amery W, Dony JA. A clinical trial design avoiding undue placebo treatment. J Clin Pharmacol 1975;15:674-9.
39. Katz N. Enriched enrollment randomized withdrawal trial designs of analgesics: Focus on methodology. Clin J Pain 2009;25:797-807.
40. Kopec JA, Abrahamowicz M, Esdaile JM. Randomized discontinuation trials: Utility and efficiency. J Clin Epidemiol 1993;46:959-71.
41. Baron R, Freynhagen R, Tolle TR, et al. The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy. Pain 2010;150:420-7.
42. Cibere J, Kopec JA, Thorne A, et al. Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. Arthritis Rheum 2004;51:738-45.
43. Crofford LJ, Mease PJ, Simpson SL, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief: A 6-month, double-blind, placebo-controlled trial with pregabalin. Pain 2008;136:419-31.
44. Friedmann N, Klutzaritz V, Webster L. Efficacy and safety of an extended-release oxycodone formulation in patients with moderate to severe osteoarthritic pain. J Opioid Management 2011;7:193-202.
45. Gilron I, Wajsbrot D, Therrien F, Lemay J. Pregabalin for peripheral neuropathic pain: A multicenter, enriched enrollment randomized withdrawal placebo-controlled trial. Clin J Pain 2011;27:185-93.
46. Hewitt DJ, Ho TW, Galer B, et al. Impact of responder definition on the enriched enrollment randomized withdrawal trial design for establishing proof of concept in neuropathic pain. Pain 2011;152:514-21.
47. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: Results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin 2011;27:151-62.
48. Alderson P, Chalmers I. Survey of claims of no effect in abstracts of Cochrane reviews. BMJ 2003;326:475.
49. D'Agostino RB, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues – the encounters of academic consultants in statistics. Stat Med 2003;22:169-86.
50. Yocum D, Fleischmann R, Dalgin P, et al. Safety and efficacy of meloxicam in the treatment of osteoarthritis. Arch Intern Med 2000;160:2947-54.
51. Layton D, Hughes K, Harris S, Shakir SAW. Comparison of the incidence rates of thromboembolic events reported for patients prescribed celecoxib and meloxicam in general practice in England using Prescription-Event Monitoring data. Rheumatology 2003;42:1354-64.

52. Distel M, Mueller C, Bluhmki E, Fries J. Safety of meloxicam. Rheumatology 1996;35:68-77.
53. Braithwaite RS, Omokaro C, Justice AC, Nucifora K, Roberts MS. Can broader diffusion of value-based insurance design increase benefits from US health care without increasing costs? In: PLoS Med; 2010.
54. Suter LG, Fraenkel L, Braithwaite RS. The cost-effectiveness of adding magnetic resonance imaging to the management of early rheumatoid arthritis. Arch Intern Med 2011;171:657-67.
55. Abraham NS, Hlatky MA, Antman EM, et al. A focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. Circulation 2010;122:2619-33.
56. Barkin RL, Buvanendran A. Focus on the COX-1 and COX-2 agents: Renal events of nonsteroidal and anti-inflammatory drugs. Am J Ther 2004;11:124-9.
57. Davies NM, Reynolds JK, Undeberg MR, Gates BJ, Ohgami Y, Vega-Villa KR. Minimizing risks of NSAIDs: cardiovascular, gastrointestinal and renal. Expert Rev Neurother 2006;6:1643-55.
58. Dieppe P, Bartlett C, Davey P, Doyal L, Ebrahim S. Balancing benefits and harms: The example of non-steroidal anti-inflammatory drugs. BMJ;329:31-4.
59. Hernandez-Diaz S, Garcia-Rodriguez LA. Epidemiologic assessment of the safety of conventional nonsteroidal anti-inflammatory drugs. Am J Med 2001;110 Suppl 3A:20S-7S.
60. Brandt C, Nadkarni P. Web-based UMLS concept retrieval by automatic text scanning: A comparison of two methods. Comput Methods Programs Biomed 2001;64:37-43.
61. Fisk JM, Mutalik P, Levin FW, Erdos J, Taylor C, Nadkarni P. Integrating query of relational and textual data in clinical databases: A case study. J Am Med Inform Assoc 2003;10:21-38.
62. Konovalov S, Scotch M, Post L, Brandt C. Biomedical informatics techniques for processing and analyzing web blogs of military service members. J Med Internet Res 2010;12:e45.
63. Womack J, Scotch M, Gibert C, et al. A comparison of two approaches to text processing: Facilitating chart reviews of radiology reports in electronic medical records. Perspect Health Inf Manag 2010;7:1a.
64. Mazzuca SA, Brandt KD, Katz BP, et al. Subject retention and adherence in a randomized placebo-controlled trial of a disease-modifying osteoarthritis drug. Arthritis Rheum 2004;51:933-40.
65. Allen KD, Renner JB, Devellis B, Helmick CG, Jordan JM. Osteoarthritis and sleep: The Johnston County Osteoarthritis Project. J Rheumatol 2008;35:1102-7.
66. Fabsitz R, Sholinsky P, Goldberg J. Correlates of sleep problems among men: The Vietnam Era Twin Registry. J Sleep Res 1997;6:50-6.
67. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: A systematic review and meta-analysis. Ann Rheum Dis 2007;66:433-9.
68. Messier SP. Diet and exercise for obese adults with knee osteoarthritis. Clin Geriatric Med 2010;26:461-77.
69. Bennell KL, Hinman RS. A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. J Sci Med Sport 2011;14:4-9.
70. Hawker GA, Mian S, Bednis K, Stanaitis I. Osteoarthritis year 2010 in review: Non-pharmacologic therapy. Osteoarthritis Cartilage 2011;19:366-74.
71. Otis JD. Managing chronic pain: A cognitive-behavioral therapy approach. New York: Oxford University Press; 2007.
72. Zhao SZ, McMillen JI, Markenson JA, et al. Evaluation of the functional status aspects of health-related quality of life of patients with osteoarthritis treated with celecoxib. Pharmacotherapy 1999;19:1269-78.
73. Boutron I, Estellat C, Ravaud P. A review of blinding in randomized controlled trials found results inconsistent and questionable. J Clin Epidemiol 2005;58:1220-6.
74. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340.
75. Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis: The Arthritis Impact Measurement Scales. Arthritis Rheum1980;23:146-52.
76. Sherbourne CD, Stewart AL. The MOS social support survey. Soc Sci Med 1991;32:705-14.
77. Rogers JC, Irrgang JJ. Measures of adult lower extremity function. Arthritis Rheum 2003;49:S80-3.
78. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis Rheum 2001;45:453-61.
79. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.

80. Dunbar MJ, Robertsson O, Ryd L, Lidgren L. Appropriate questionnaires for knee arthroplasty: Results of a survey of 360 patients fom the Swedish knee arthroplasty registry. J Bone Joint Surg Br 2001;83:339-44.
81. Brazier JE, Harper R, Munro J, Walters SJ, Snaith ML. Generic and condition-specific outcome measures for people with osteoarthritis of the knee. Rheumatology 1999;38:870-7.
82. Ryser L, Wright BD, Aeschlimann A, Mariacher-Gehler S, Stucki G. A new look at the Western Ontario and McMAster Universities Osteoarthritis Index using rasch analysis. Arthritis Rheum 1999;12:331-5.
83. Angst F, Aeschlimann A, Steiner W, Stucki G. Responsiveness of the WOMAC Osteoarthritis Index as compared with the SF-36 in patients with osteoarthritis of the legs undergoing a comprehensive rehabilitation program. Ann Rheum Dis 2001;60:834-40.
84. Bellamy N, Campbell J, Hill J, Band P. A comparative study of telephone versus onsite completion of the WOMAC 3.0 osteoarthritis index. J Rheumatol 2002;29:783-6.
85. Allen KD. The value of measuring variability in osteoarthritis pain. J Rheumatol 2007;34:2132-3.
86. Hawker GA. Experiencing painful osteoarthritis: What have we learned from listening? Curr Opin Rheumatol 2009;21:507-12.
87. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology 2003;28:916-31.
88. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994;47:81-7.
89. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 2003;106:337-45.
90. King A, Daniels J, Lim J, Cochrane DD, Taylor A, Ansermino JM. Time to listen: A review of methods to solicit patient reports of adverse events. Qual Safety Health Care 2010;19:148-57.
91.Carroll, K.M., Nich, C., Sifry, R., et al. A general system for evaluating therapist adherence and competence in psychotherapy research in the addictions. Drug and Alcohol Dependence 2000, 57:225-38.
92. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharm Ther 1981;30:239-45.
93. Woodworth T, Furst DE, Alten R, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II. J Rheumatol 2007;34:1401-14.
94. Strand V, Kelman A. Outcome measures in osteoarthritis: Randomized controlled trials. Curr Rheumatol Reports 2004;6:20-30.
95. Rubin DB. Multiple imputation after 18+ years (with discussion). J Am Stat Assoc 1996:473-89.
96. Schafer JL. Analysis of incomplete multivariate data. London: Chapman & Hall; 1997.
97. Scott Long J. Regression models for categorical and limited dependent variables. Advanced quantitative techniques in the social sciences: Sage Publications; 1997.
98. Jones BL, Nagin DS. Advances in group-based trajectory modeling and an sas procedure for estimating them. Sociol Methods Res 2007;35:542-71.
99. Lane P. Handling drop-out in longitudinal clinical trials. Pharmaceutical Stat 2008;7:93-106.
100. Feeny D, Furlong W, Torrance GW, et al. Multiattribute and single-attribute utility functions for the Health Utilities Index Mark 3 system. Med Care 2002;40:113-28.
101. Grootendorst P, Feeny D, Furlong W. Health Utilities Index Mark 3: Evidence of construct validity for stroke and arthritis in a population health survey. Med Care 2000;38:290-9.
102. Luo N, Johnson JA, Shaw JW, Coons SJ. Relative efficiency of the EQ-5D, HUI2, and HUI3 Index scores in measuring health burden of chronic medical conditions in a population health survey in the United States. Med Care 2009;47:53-60.
103. Gold MR, Siegel JE, Russell LB, Weintstein MC. Cost effectiveness in health and medicine. New York: Oxford University Press;1996.
104. Phibbs CS, Bhandari A, Yu W, Barnett PG. Estimating the costs of VA ambulatory care. Med Care Res Rev 2003;60:54S-73S.
105. Turner JA, Clancy S. Comparison of operant-behavioral and cognitive-behavioral group treatment for chronic low back pain. J Consulting Clin Psychol 1990;58:573-9.
106. Paykel ES, Scott J, Cornwall PL, et al. Duration of relapse prevention after cognitive therapy in residual depression: Follow-up of controlled trial. Psychological Med 2005;35:59-68.

107. Decision making in health care: Theory, psychology, and applications. New York: Cambridge University Press; 2003.
108. Krahn MD, Naglie G, Naimark D, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Analyzing the model and interpreting the results. Med Decis Making 1997;17:142-51