PAIN OUTCOMES COMPARING YOGA VERSUS STRUCTURED EXERCISE

NCT01797263

MAY 15, 2017

A. RESEARCH OBJECTIVES

Fibromyalgia is a chronic pain disorder characterized by widespread pain, multiple tender points, abnormal pain processing, sleep disturbances, fatigue, and often psychological distress.[1] Individuals are often afflicted with fibromyalgia symptoms for years. For those with severe symptoms, fibromyalgia can be extremely debilitating and interfere with basic daily activities. Although numerous treatments are available for the management of fibromyalgia and some have showed initial promise, no treatment has demonstrated convincing effectiveness. Thus, management is difficult for clinicians.

Fibromyalgia is common; affecting an estimated 10 million Americans--approximately 3%-5% of the general population.[2] Perhaps because fibromyalgia affects more women than men, little is known about fibromyalgia in men or veterans. Eisen et al. found that fibromyalgia was diagnosed almost twice as frequently in Gulf War Veterans compared to non-Gulf War Veterans.[3] The prevalence in Iraq and Afghanistan War Veterans has not yet been reported. If the 2010 American College of Rheumatology (ACR) diagnostic criteria are applied,[4] which do not require tender point examination, the prevalence of fibromyalgia in men rises significantly.[5] Two reasons explain the projected increase in fibromyalgia prevalence among veterans. First, the 2010 ACR diagnostic criteria for fibromyalgia have gained wider use and acceptance. Second, the number of women veterans is expected to comprise over 10% of the total veteran population by 2020.[6]

Medications are often the first line of therapy for fibromyalgia, but are frequently associated with adverse effects and show modest treatment benefits in clinical trials and practice.[7] Aerobic exercise programs have proven benefit, but adherence to exercise is difficult to maintain and can lead to exercise-induced pain and myalgias if performed incorrectly. While the literature supports psychological treatments such as cognitive behavioral therapy (CBT) for reducing the overall symptoms of fibromyalgia, access to therapists with fibromyalgia expertise is limited. For relief, patients often turn to complementary and alternative medicine when traditional treatments are not effective.[8] Yoga has shown initial promise for relief of fibromyalgia symptoms; presumably because yoga combines the benefits of exercise with relaxation and mindfulness practices. However, few yoga studies in fibromyalgia exist and those conducted have involved small sample sizes and yoga has not been compared to other treatments. With these challenges and limitations in mind, research to develop and compare different treatments for fibromyalgia, especially in veterans, is urgently needed.

We believe other treatment options are needed when pharmacological management fails to relieve fibromyalgia symptoms for veterans. Our long-term research objective is to develop, test, and implement novel treatments that address barriers to effective fibromyalgia treatment and that can be practicably applied in VA care settings. The **P**ain **O**utcomes comparing **Y**oga versus **S**tructured **E**xercise **(POYSE)** Trial is a 2-arm parallel group, randomized clinical trial. The POYSE trial will target ***306 veterans*** with fibromyalgia and will compare the effectiveness of a yoga-based intervention (YOGA) with that of a structured exercise program (SEP). The trial will last 9-months and participants will undergo comprehensive outcome assessments at baseline, ***1, 3, 6, and 9 months***.

Study Aims:

1) **To compare the interventions' (YOGA vs. SEP) effects on overall fibromyalgia severity at 1 month (*early response*), 3 months (immediate post-intervention) and at *6 and 9 months (sustained effects)***
2) **To compare the interventions' effects on specific fibromyalgia symptoms (pain, sleep, fatigue), functional impairment, and related outcomes (quality of life, depression, anxiety)**
3) **To compare the cost-effectiveness of the interventions**

Our primary hypothesis is that the yoga intervention will be more effective than a structured exercise program in reducing overall fibromyalgia severity as measured by the Fibromyalgia Impact

Questionnaire-Revised (FIQR); a global measure of fibromyalgia symptoms.[9] *Our secondary hypotheses* is that yoga will be more effective than a structured exercise program in improving secondary outcomes including functional impairment, pain intensity, sleep quality, fatigue, quality of life, depression, and anxiety.

The trial is powered to detect a clinically significant between-group treatment effect. Based on our pilot work and studies from other research groups, we expect both treatment arms to significantly improve fibromyalgia outcomes at all outcome assessment time points ***(1, 3, 6, and 9 months)*** compared to baseline. In addition to determining whether there is differential clinical effectiveness between the two treatments, their relative cost-effectiveness will be determined.

B. BACKGROUND

B1. Fibromyalgia is common, costly, and associated with frequent health care use

Fibromyalgia affects at least 3%-5% of the general population[10] or approximately 10 million Americans. In clinical populations, the prevalence of fibromyalgia exceeds 15%.[11] Women account for more than 80% of affected individuals. The economic burden to society from fibromyalgia-related lost productivity and disability is substantial. Sixteen percent of individuals with fibromyalgia reported receiving Social Security disability payments compared to 2.2% of the non-retirement US adult population.[12] Analysis of administrative claims data from a large, Fortune 100 company showed that the total annual cost for fibromyalgia claimants was $5,945 versus $2,486 for other beneficiaries.[13]

Patients with fibromyalgia are frequent users of health care resources; comparable to those with diabetes mellitus and hypertension.[14] On average, those with fibromyalgia have 10 outpatient medical visits per year.[15] When “nontraditional treatments” are considered, this number increases to approximately one visit per month.[15] The mean yearly per-patient cost in 1996 dollars was $2,274.[15] Almost 50% of hospitalizations are related to fibromyalgia symptoms. Compared with patients with other rheumatologic disorders, those with fibromyalgia are more likely to have lifetime surgical interventions, including back or neck surgery, appendectomies, carpal tunnel release, gynecologic and abdominal surgeries, and tonsillectomies.[15]

B2. Fibromyalgia is associated with significant morbidity and possibly mortality

In terms of quality of life, persons with fibromyalgia consistently score low in multiple domains of mental and physical functioning, similar to patients with chronic obstructive pulmonary disease (COPD) and diabetes.[16-18] Compared to patients with multiple sclerosis or rheumatoid arthritis, patients with fibromyalgia report greater fatigue, pain, depression, and anxiety.[19] In fact, 20%-40% of fibromyalgia patients have a comorbid depressive disorder.[20-23]

Intriguing reports have suggested that chronic widespread pain and fibromyalgia are associated with increased mortality. When compared to subjects without pain, persons with chronic widespread pain in the community had an increased mortality risk (mortality rate ratio 1.31; 95% CI, 1.05-2.19).[24] In a cohort study from Denmark, Dreyer et al reported an excess mortality risk of 30% (standardized mortality ratio 1.3; 95% CI, 0.9-1.7) in those with fibromyalgia.[25] Using population mortality rates to compare, Wolfe et al also found an excess mortality risk (standardized mortality ratio of 1.45 (95% CI, 1.19-1.86)).[26] It is hypothesized that unhealthy lifestyle behaviors, including lack of exercise, explains this association between fibromyalgia and increased mortality.[27]

B3. Fibromyalgia studies of veterans is limited

Epidemiologic studies[28,29] have assessed fibromyalgia prevalence and other symptom-based conditions among Gulf War Veterans. Buskila et al.[29] found 17% of Gulf War Veterans with soft tissue rheumatism also had concomitant fibromyalgia; representing a much higher prevalence than seen in previous studies of military populations. In the Iowa Persian Gulf Study, fibromyalgia symptoms were reported by 18%-24% of Gulf War Veterans relative to 9%-13% of non-deployed personnel.[28] Eisen et al[3] found that a diagnosis of fibromyalgia was twice as prevalent in deployed vs. non-deployed Gulf War Veterans.

Another study examined health care utilization and found that Gulf War Veterans were at an increased risk of postwar hospitalization for fibromyalgia.[30] The prevalence in Iraq and Afghanistan War Veterans has not yet been reported. Beyond these epidemiologic studies focused on Gulf War veterans with fibromyalgia, research in veteran populations is limited. A potential explanation for this paucity of research is the perception that fibromyalgia is relatively uncommon in men. Although fibromyalgia in men is largely unexplored, one study of men with fibromyalgia found they had more severe symptoms, worse physical function, and lower quality of life[31] than women with fibromyalgia. In this context, studies that focus on relieving the suffering of veterans with fibromyalgia are imperative.

B4. Medications are the most common treatments for fibromyalgia, but have modest benefits

Medications for fibromyalgia are largely targeted at its symptoms, especially depression, sleep disturbance and muscle pain. Tricyclic anti-depressants, selective serotonin reuptake inhibitors (SSRI), skeletal muscle relaxants, analgesics, dual reuptake inhibitors (SNRIs), anticonvulsants, and dopamine agonists have been used with some success.[1] In 2007, the Federal Drug Administration approved Lyrica (pregabalin) as the first medication to treat fibromyalgia. Cymbalta (duloxetine) was approved in 2008; and Savella (milnacipran) was approved in 2009.

Despite some success with currently used medications, only one-third of patients in most trials who receive the active drug achieve a clinically meaningful improvement in their symptoms.[32-34] There is evidence that fibromyalgia medications provide short-term (i.e. 8 to 12 weeks) improvements in symptoms,[32-36] but given the chronic nature of fibromyalgia, more studies are needed to determine whether improvements are maintained over months or years. Patients used a mean of 2.7 fibromyalgia-related medications;[15] demonstrating the numerous therapies tried and the challenging nature of fibromyalgia treatment. Qualitative research has found that patients with fibromyalgia perceive that they are given multiple treatments without any chance for a cure.[37]

B5. Psychological therapies are helpful, yet not always available or acceptable

Psychological and behavioral interventions have proven efficacy for fibromyalgia.[38-40] Cognitive-behavior therapy (CBT) is the most evidence-based psychological alternative to traditional medical approaches to fibromyalgia management. The benefits of CBT likely stem from its ability to intervene in the complex interplay of pathophysiology, cognition, affect, and behavior that is thought to drive pain and suffering. While CBT has proven efficacy, it is not yet widely available in many care settings, even in the VA despite mental health integration initiatives. Barriers to implementation are largely administrative and systemic and include time constraints, lack of knowledge in cognitive and behavioral strategies, and limited availability of specialists to deliver behavioral treatments. Many mental health professionals lack experience in applying CBT to medical conditions[41] in general and fibromyalgia specifically. Furthermore, CBT may not be acceptable to many patients who fear the stigma of contact with mental health clinicians.

B6. Aerobic exercise is effective, but adherence and exercise-induced pain are challenges

Two systematic reviews[42,43] and one meta-analysis[44] support the effectiveness of supervised aerobic exercise for fibromyalgia. Randomized controlled trials have demonstrated that supervised aerobic exercise consistently improved physical function, especially physical fitness, well-being, and reduced tender point pain.[45-49] Rossy et al reported that a physically based treatment for fibromyalgia had an effect size of 0.7 ($p<0.05$) for physical function improvement and 0.4 ($p<0.05$) for associated symptoms.[44] Almost all the published exercise trials involved ≥ 12 weeks of supervised exercise program provided by a physiotherapist (or exercise physiologist) with expertise in fibromyalgia. At adequate intensity, various types of aerobic exercise (e.g. cycling, walking, jogging and pool aerobic exercises) have all been shown to reduce the symptoms of fibromyalgia.[47-51]

Individuals who consistently exercise are most likely to experience benefits, both in symptoms and daily function. The major limiting factor to exercise programs is adherence. After the supervised phase of an exercise program, exercise adherence declines and fibromyalgia symptoms worsen. Commonly cited

reasons for non-adherence are: time limitations, family commitments, the impact of other comorbidities, increased stress and exercise-induced pain or myalgias.

B7. Other treatments are needed when fibromyalgia symptoms are not relieved

The lack of relief from existing treatments is frustrating to patients who may feel like they have exhausted all options in their fibromyalgia treatment. This is also frustrating for VA providers concerned about the limited efficacy of medications and lack of additional treatment options. Therefore, novel treatment approaches that have potential for application across multiple VA clinical settings are needed to supplement existing services for fibromyalgia care. Increasingly, patients are interested in complementary and alternative medicine (CAM) treatment options.[8] This growing interest in CAM is likely multifactorial, involving concerns about limited efficacy of conventional medicine, adverse effects of medications, and avoidance-beliefs related to medications or mental health treatments.[8] CAM treatment options typically have minimal physical and emotional risks, and may allow patients to take a more active role in managing their illness.[8]

B8. Yoga holds promise for fibromyalgia as it combines exercises and mental techniques

Yoga therapy is defined by the International Association of Yoga Therapists as "the process of empowering individuals to progress toward improved health and well-being through the application of the philosophy and practice of yoga".[52] Yoga therapy attempts to incorporate yoga principles into a health regimen addressing health-related issues ranging from physical, psychological, and emotional health.[53] The various styles of yoga that people use for health purposes typically combine physical postures, breathing techniques, and meditation or relaxation. The therapeutic effect of yoga is presumed to be related to the combination of postures, breathing strategies, and relaxation/meditation techniques; the combination is believed to be more beneficial than simple exercise alone.[54] Because of the active mind-body component, it is believed that yoga is more effective than traditional exercise.[55-57]

B10. Yoga is effective for chronic musculoskeletal pain, especially chronic low back pain

Williams et al[58] conducted a trial to evaluate the effects of Iyengar yoga on chronic low-back pain outcomes. The intervention patients attended 90-minute Iyengar yoga classes twice a week for 12-weeks. Compared to the usual control arm, the yoga group had significantly greater reductions in functional disability, pain, and depression at weeks 12 and 24, and at 6-months. There were no significant differences in pain medication use between the groups. Groessl et al. examined the benefits of 10 weeks of yoga for veterans with chronic low-back pain.[59] Significant improvements were found for pain depression, energy/fatigue, and mental health. In a recent and relatively large trial (N = 228), Sherman and colleagues,[60] compared 12 weekly classes of either viniyoga-style yoga (emphasizing postures, breathing exercises, and guided deep relaxation) or conventional stretching exercises, or a self-care book. At 12 weeks, participants in the yoga group had greater improvement of symptoms and function than those in the self-care group. At 26 weeks, the yoga group sustained greater improvement in function over the self-care group. However, yoga was not superior to stretching exercises.[60]

B11. Pilot studies and a meta-analysis suggest that yoga may be effective for fibromyalgia

Several pilot studies have shown that yoga reduces fibromyalgia pain[61-63] and improves maladaptive pain beliefs such as catastrophizing.[61] The most methodologically rigorous study of yoga in fibromyalgia was conducted by Carson et al.[61] In this trial, 53 fibromyalgia patients were randomized to an 8-week yoga program (gentle poses, meditation, breathing exercises, yoga-based coping instructions, and group discussions) or to wait-list control. At post-treatment, patients assigned to the yoga program significantly improved on fibromyalgia symptoms and functioning, including pain, fatigue, and mood, and in pain catastrophizing, acceptance, and other coping strategies. In a literature review examining the health benefits of yoga vs. exercise, the authors concluded that yoga interventions appeared to be equal or superior to exercise in nearly every outcome measured except those involving physical fitness and called for future trials to examine the distinctions between yoga and exercise.[61]

Carson et al conducted an 8-week yoga exercise pre- and post-intervention study on 58 fibromyalgia subjects.[64] Seven of the 58 subjects agreed to undergo pressure pain threshold assessment pre- and

post-intervention. At the end of the study, subjects (n=7) reported significant improvements in the FIQ-revised total score (-30.7%), pain intensity (-51.2%) and strength (+21.3%), as well as, a significant increase in the pressure pain threshold (+21.3%).[64] This study suggests yoga's effect on pain sensitivity and some of the underlying mechanisms of pain relief in fibromyalgia.

In a recent meta-analysis of the efficacy and safety of meditative movement therapies (Qigong, Tai Chi, and Yoga), Langhorst et al.[65] found that yoga led to significant improvements in pain, fatigue, depression and quality of life. In addition, these treatments are safe leading to minimal drop-out rates (3.1%) because of adverse events. The authors called for higher quality studies with larger samples and comparisons of these therapies with established treatments.[65]

B12. A trial comparing yoga vs. structured exercise for fibromyalgia is timely and needed

While there is trial evidence supporting both yoga and structured exercise, these approaches have not been compared against each other. The current POYSE trial design is a significant step beyond previous fibromyalgia trials. We believe a head-to-head comparative effectiveness study design best answers the question of how to most effectively treat fibromyalgia, especially for veterans' refractory to other treatments. In addition, patients frequently differ in their treatment preferences, and a trial to determine the clinical effectiveness and cost-effectiveness of two evidence-based treatment options for fibromyalgia has immense importance. This population of veterans is particularly challenging to VA providers and alternative treatments are critically needed.

B13. Our prior pain research that informs this POYSE trial

We have performed numerous clinical trials and preliminary studies that demonstrate our team's experience and expertise in three relevant areas: 1) management of musculoskeletal pain in veterans; 2) conduct of clinical and translational fibromyalgia studies; and 3) design and test of yoga- and exercise based interventions in patients with fibromyalgia and other medical conditions. Cumulatively, this body of research (summarized below) informs the POYSE trial:

Stepped Care for Affective Disorders and Musculoskeletal Pain--SCAMP trial: Our National Institute of Mental Health funded SCAMP trial tested antidepressants combined with a pain self-management program delivered by nurse care managers, showed the intervention group (n = 123) experienced large improvements in depression severity (effect size = 1.1) as compared to usual care patients (n = 127) and moderate improvements in pain severity (effect size = 0.5).[66]

Evaluation of Stepped Care for chronic Pain--ESCAPE Trial: We are actively preparing manuscripts for the VA RR&D-funded ESCAPE trial. ESCAPE is comparing a combination of pain treatments, including algorithm-based analgesics, pain self-management skills, and cognitive behavioral training, versus usual care. The stepped-care intervention is targeting OEF/OIF/OND veterans with musculoskeletal pain of the spine (low back, neck) and extremities (legs, knees, hips, and shoulders). Recruitment of the 242 subjects was completed in May 2011 and follow-up of patients in March 2012. The ESCAPE study is significant because it is the first trial testing a novel combination of chronic pain treatments in the newest cohort of returning veterans. Two baseline ESCAPE papers have been published so far.

The Care Management for the Effective use of Opioids (CAMEO) trial was recently funded by VA HSR&D. We have recruited 55 patients to date. CAMEO is a two arm randomized trial to compare the effectiveness of pharmacological vs. behavioral approaches for veterans with chronic low back pain who are currently receiving chronic opioid therapy.

Chronic widespread pain among returning Gulf War Veterans: In our study of predictors of incident chronic widespread pain in 602 Gulf War Veterans, 19% developed chronic widespread pain at follow-up. A positive family history of medically unexplained persistent symptoms [odds ratio (OR) = 4.8 (2.3, 13.2)] was strongly associated with chronic widespread pain. At baseline, individuals reporting preexisting symptoms of bronchitis [OR=4.9 (1.9, 12.3)] and cognitive dysfunction [OR= 2.1 (1.1, 4.2)] were more likely to develop chronic widespread pain. Rather than combat-related exposure, the perception of stress during the Gulf War [OR=1.6 (1.1, 2.3)] correlated with chronic widespread pain.[67]

A Pilot Study of Exercise-based Motivational Interviewing for Patients with Fibromyalgia tested the feasibility and acceptability of a supervised exercise program coupled with telephone-delivered motivational interview counseling to promote exercise adherence.[68] As assessed by the Fibromyalgia Impact Questionnaire, physical impairment and pain improved significantly at 12- and 30- weeks, as did the number of exercise minutes per week. The number of exercise minutes was significantly associated with reduced physical impairment (r=-0.57, p=0.01).

A Randomized Controlled Trial of Exercise-based Motivational Interviewing for Fibromyalgia—For this NIAMS-funded trial, 216 patients with fibromyalgia were randomized to 6 motivational interviewing sessions (n =107) or an educational control arm consisting of 6 fibromyalgia self-management lessons (n = 109).[69] The intervention arm was superior to the educational control in increasing the number of hours of physical activity and pain reduction immediately post-intervention and at 3-month follow-up. In addition, more intervention patients than controls improved in FIQ-physical impairment scores and 6-minute walk test measurements (43.9 (SD=6.3) vs. 24.8 meters (6.3), p=0.03) at follow-up.

Yoga interventions for caregivers: We tested an 8-week yoga program with informal (family or friends) caregivers.[70] Caregivers were randomized to a yoga intervention (n=8) or control group (n=9). Those receiving the yoga intervention demonstrated significantly increased lower body strength with trends for improved coping, upper body strength, and aerobic endurance.[70]

Yoga interventions for breast cancer survivors: We also studied an 8-week yoga intervention in 40 breast cancer survivors and found significant increases (compared to the attention control group) in: lower body flexibility; side flexibility; lower body strength; and hand grip strength in the yoga group. The yoga group also demonstrated improved pain relief, stress reduction, and increased confidence.[71]

A Yoga intervention to reduce fear of falling: We completed a yoga study to manage fear of falling in 14 older adults.[72] Participants showed a decrease in fear of falling, an increase in static balance, and a large improvement in lower body flexibility. This was the first study to examine the effect of yoga on fear of falling and balance in older adults. Given the frequent complaint of falling among patients with fibromyalgia, yoga interventions may have the potential additional benefits of preventing falls.

Yoga for veterans with stroke: We recently completed VA QUERI-funded pilot study of 8 weeks of yoga for veterans with chronic stroke.[73] In this study, we developed a standard yoga-based rehabilitation protocol with postures and breathing exercises in sitting, standing, and supine positions. Programming included mindfulness meditation and the protocol was tailored to consider physical abilities and activity tolerance of participants. Individuals at least 6 months post-stroke (n=45) were randomized 3:1 to yoga or wait list control. In within-group analyses, individuals in the yoga arm had significant improvement between baseline and 8 weeks in: pain, balance; range of motion; gait speed; walking endurance; balance self-efficacy; activity and participation; quality of life; and stroke related disability.

C1. SIGNIFICANCE AND RELEVANCE TO VHA PATIENT CARE MISSION

Pain is a critical health problem among veterans. Chronic pain affects 40%-70% of veterans[74] and is a leading cause of disability, with substantial impact on millions of veterans' lives. Pain was the most frequently reported symptom in Persian Gulf War Veterans[75] and is expected to be even more prevalent in the current cohort of veterans.[76] The effect of chronic widespread pain and fibromyalgia is far reaching, affecting society in terms of economic costs and lost work productivity and on fibromyalgia patients, in symptom burden, decreased physical functioning and perhaps even increased mortality.

The VA has pioneered innovative organizational efforts, such as "Pain as the 5th Vital Sign" initiative[77] and the VHA National Pain Management Strategy in an effort to address pain among veterans. The VHA National Pain Management Strategy was initiated in 1998,[78] and established pain management as a national priority. The overall objective of the national strategy is to develop a comprehensive, multicultural, integrated, system-wide approach to pain management that reduces pain and suffering for veterans experiencing acute and chronic pain associated with a wide range of conditions, including terminal illness. Central to this objective is to assure access to an interdisciplinary pain care across VA facilities. Comparing the effectiveness of different approaches to treat fibromyalgia is critical in meeting strategy objectives. Despite the rising prevalence and negative impact of fibromyalgia, few intervention studies have addressed this condition in veterans. It is in this context that the POYSE trial is proposed.

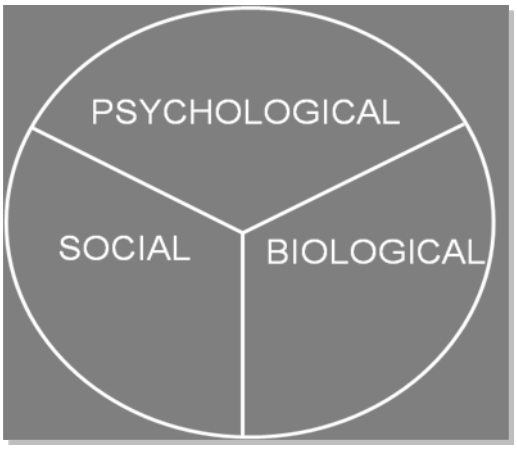
Given the modest effectiveness of current treatments and the burden fibromyalgia places on veterans and clinicians, our research proposal is significant in several regards. *First*, the POYSE trial directly addresses a high priority area for the VA and is well aligned with the VHA Pain Management Strategy and VHA Pain Management Directive 2009-053. *Second*, because previous fibromyalgia studies have included more than 90% women, our trial will provide information vital to begin filling an evidence vacuum regarding comparative effectiveness of treatments for fibromyalgia, especially men with fibromyalgia. *Third*, POYSE will extend our current understanding of non-pharmacological treatments for fibromyalgia. *Fourth*, the economic evaluation will provide useful information to VA administrators and managers to inform clinical implementation decisions.

D. RESEARCH DESIGN AND METHODS

D1. Conceptual Model for POYSE Trial

The management of fibromyalgia is complex. As a result, specialists such as rehabilitation therapists, orthopedists, anesthesiologists, rheumatologists, and neurologists, are often consulted. This common practice of referring patients with fibromyalgia to specialists with a relatively narrow focus compromises the effort to address whole-person care that employs a biopsychosocial approach-- an approach that seems best suited for rehabilitation settings in the VA.

Figure 1: Biopsychosocial Model



The biopsychosocial model posits that the causes and outcomes of many illnesses involve the interaction of physical and physiological factors, psychological traits and states, and social-environmental factors. Effective pain management accounts for these factors. The biopsychosocial model **(Figure 1)** is the most widely accepted conceptual model in pain medicine.[79] Comprehensive management based on the biopsychosocial model of pain generation and perception improves outcomes.[80] Such management focuses on the interplay among biological, psychological, and social factors that underlie the interventions to be tested and the key outcome domains to be assessed in POYSE.

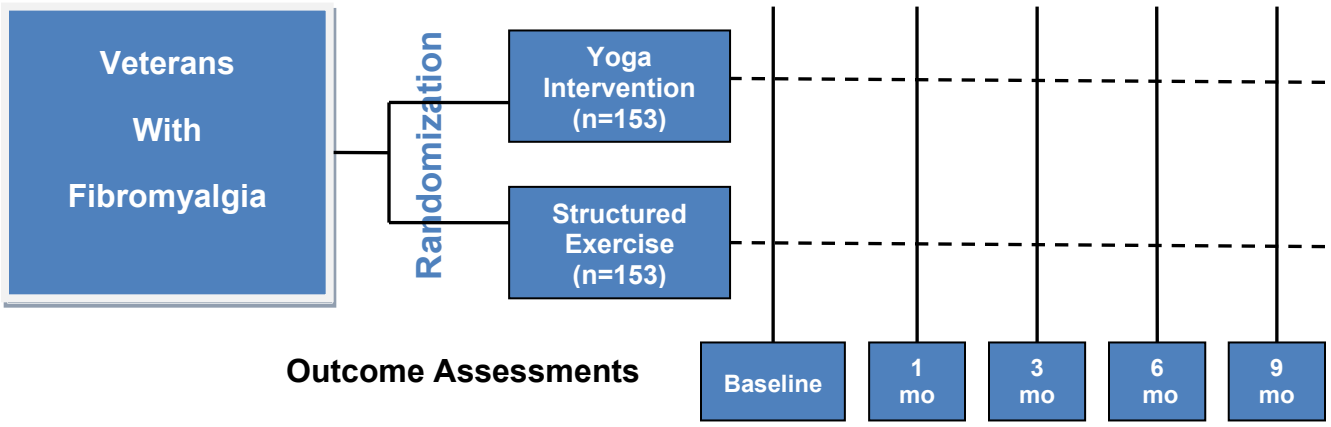
Applied to POYSE, the yoga-based intervention and structured exercise program will not simply address the **biological** or physical experience of fibromyalgia. Rather, POYSE interventions will be individually tailored taking into account how **psychological** and **social** factors influence function, pain severity, sleep quality, quality of life, and psychological symptoms.

D2. OVERALL DESIGN

Our study sample will include ***306 veterans*** with fibromyalgia. Patients from the five primary care clinics and rheumatology clinic at the Roudebush VA Medical Center (RVAMC) and ***three*** community based outpatient clinics (Terre Haute, ***Martinsville***, and Bloomington CBOCs) will be recruited to participate. The **P**ain **O**utcomes comparing **Y**oga vs. **S**tructured **E**xercise **(POYSE)** study will be a 2-arm, parallel group, randomized comparative effectiveness trial. After eligibility determination and informed consent procedures, participants will be randomized to one of two study arms. The YOGA arm will involve a standardized 12-week, yoga-based intervention and will consist of three treatment components: 1) in-person group yoga taught by a yoga therapist; 2) a relaxation audio recording for home-use; and 3) a DVD recording to reinforce concepts taught during in-person sessions. Patients randomized to the structured exercise program (SEP) arm will participate in a 12-week exercise program delivered in a group/class format and supervised by a fitness instructor. In addition, SEP patients will receive a DVD (for home use) demonstrating aerobic, strengthening, and stretching exercises for fibromyalgia, a one-on-one consultation session with the fitness instructor, and supervised exercise sessions for 12 weeks. **Figure 2** shows the POYSE trial design.

The intervention period will last for 3 months, after which time patients will be followed for an additional 6 months (total of 9 months). Treatment response will be assessed at ***1, 3, 6, and 9 months after the date of the first intervention session.*** The primary end point will be at 3 months (immediate post-intervention). Early response will be assessed at 1 month. Sustained response will be assessed at 6 and 9 months post-randomization. POYSE will last 4 years including 3 months for start-up; 2.5 years for recruitment; ***9 months*** for follow-up; and 6 months for data analysis and manuscripts.

Figure 2: POYSE Trial Design



D3. STUDY SITES

The RVAMC is an urban, university-affiliated, tertiary care center in Indianapolis which provides health care for more than 53,000 veterans. As Indiana's tertiary care facility, RVAMC receives referrals from VA facilities at Ft. Wayne and Marion, Indiana, and from nearby Danville, Illinois. The RVAMC provides acute inpatient medical, surgical, psychiatric, neurological, and rehabilitation care, as well as primary and specialty outpatient services. The clinics staff 75 primary care providers (faculty and resident physicians; advance practice nurses), caring for over 20,000 patients who make over 65,000 visits per year. The RVAMC is also the parent facility to three community based outpatient clinics—the Bloomington, Terre Haute, and Martinsville Outpatients Clinics. The Bloomington and Terre Haute CBOCs staff 4 primary care providers each and 1 provider is based at Martinsville. Each site provides primary care, prescription and other services to approximately 9,500 veterans in the Bloomington, Terre Haute, and Martinsville, IN metropolitan areas (all sites approximately 1 hour drive from Indianapolis).

D4. RECRUITMENT

To plan for recruitment and assess feasibility, we conducted a search of CPRS to determine the number of RVAMC veterans with a primary or secondary diagnosis of fibromyalgia (ICD-9 729.1). We identified *8,457* unique veterans. Based on our SCAMP and ESCAPE trials, we have found that > 50% who meet the initial feasibility criteria also meet our study eligibility requirements, which will give us a potential population of over *4,200* patients from which to recruit ***306 participants***. Given that we are using the 2010 American College of Rheumatology[4] diagnostic criteria for fibromyalgia, which is less restrictive than the 1990 criteria (i.e. does not require 11 of 18 tender points on examination), we expect to achieve our recruitment goals and sample size without much difficulty. In fact, > 60% of the 242 ESCAPE participants would meet the new 2010 ACR fibromyalgia criteria.

We have successfully enrolled patients for several moderately sized trials at our medical center. For example, in the SCAMP trial we successfully recruited over 65% of participants contacted in the VA. In our CRAFT study, 100 (84%) of 119 eligible veterans who were approached were successfully enrolled. In our "Pain as the 5th Vital Sign" pilot study, 159 (77%) of 206 participants surveyed expressed a willingness to participate in a clinical trial to treat their pain if offered such an opportunity. Based on these prior successes, we anticipate no difficulty meeting our sample size requirements. In terms of

retention, we assessed 87% (217/250) of SCAMP participants at 6 months and 82% of participants (205/250) at 12 months.[66] In the ESCAPE trial, we have assessed 91% (219/242) of veterans at 3 months and 91.7% at 9 months.

Consistent with previous studies conducted at RVAMC, the study sample will include at least 15% minorities, thus reflecting the demographics of our medical center. In our SCAMP study, Blacks comprised 16% of the veteran sample and 13% in ESCAPE. We do not plan to over-sample Blacks (or other minorities) or power sufficiently to explore racial differences in treatment response. The racial/ethnic composition of RVAMC and participating CBOCs makes exploring racial differences in treatment response impractical unless we employed special efforts to recruit minorities other than Blacks. In ESCAPE, we have recruited 12.5% women, but expect an even higher proportion of women to participate in POYSE given its focus on fibromyalgia.

D5a. Identifying and Enrolling Potential Participants

Providers will be informed of POYSE study details and will be asked to provide signed approval so that our team may contact their potentially eligible patients for participation in the trial. The POYSE research team, not the providers, will determine eligibility by applying the inclusion/exclusion criteria to potential participants during an "eligibility interview." In our previous trials, over 95% of physicians contacted agreed to allow us to approach their patients. Potential participants will primarily be identified by querying the VA's electronic medical record system, CPRS (Computerized Patient Record System), to create a master list of veterans who meet the following criteria: 1) fibromyalgia diagnosis (ICD9 code 729.1); 2) clinic visit in past 2 years; and 3) moderate pain severity (pain severity score ≥ 5 out of 10).

This list of potential participants will be updated monthly during the enrollment period and a recruitment letter, signed by their provider, will be mailed to qualifying veterans to describe the study. Potential participants will be contacted by phone within a week after receipt of the letter to assess eligibility and determine their interest in participating. If the veteran is eligible, an appointment will be scheduled to obtain a signed informed consent statement, HIPAA authorization from and VA consent for use of picture and/or voice those who desire to participate. The baseline interview and assessments will be conducted by research assistants blinded to treatment allocation.

This method of identifying potential study subjects through CPRS and contacting them for possible study participation has been approved by both our university IRB and VA Scientific Review Committee for the SCAMP (which enrolled 200 veterans) and ESCAPE trials (which enrolled 242 veterans). A second method, if needed, will be in-clinic contact of potential subjects by cross-referencing the CPRS list with the weekly appointment roster for each participating VA provider. A third method is self-referral by patients responding to study advertisement displayed in hospital elevators and primary care, rheumatology, and rehabilitation clinics.

D5b. Eligibility

Veterans will be eligible if they have: 1) 2010 American College of Rheumatology (ACR) diagnostic criteria **(Table 1 below)** for fibromyalgia;[4] 2) moderate pain severity ("current" pain severity score ≥ 5 out of 10); 3) stable doses of fibromyalgia medications for at least 4 weeks; and 4) access to a working telephone. *Exclusion criteria will include*: 1) severe medical conditions in which exercise is contraindicated; 2) active psychosis; 3) schizophrenia; 4) active suicidal ideation; 5) moderate to severe cognitive impairment; and 6) involvement in ongoing yoga classes or moderately intense (brisk walking) exercise program in the previous 3 months.. Access to a telephone (home or mobile) is required because most of the outcome assessments will be conducted via phone.

Exclusion criteria will be determined during the baseline eligibility survey conducted by our study team (not the patient's providers) and are designed to eliminate potential participants for whom the proposed interventions are inappropriate or unsafe and/or for whom there may be disincentives for improvement. These include severe medical conditions that may limit participation: (1) significant cardiovascular disease: New York Heart Association functional class 3 or 4 congestive heart failure; systolic blood pressure ≥ 180 or diastolic blood pressure ≥ 105 mmHg; myocardial infarction, stroke, or transient

ischemic attack (TIA) within 6 months; chest pain or dizziness with exercise; (2) COPD or asthma needing home oxygen; (3) cancer (other than skin cancer) receiving treatment or treatment planned in the next 6 months; (4) at least moderately severe cognitive impairment defined by a 6-item screener.[81]

Table 1. 2010 ACR Fibromyalgia Diagnostic Criteria

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

1. Widespread Pain Index (WPI) ≥ 7 and Symptom Severity Scale (SS) ≥ 5 OR WPI 3-6 and SS ≥ 9
2. Symptoms have been present at a similar level for at least 3 months
3. The patient does not have a disorder that would otherwise explain the pain

For full criteria: See Wolfe et al. citation [4]

D6. RANDOMIZATION

Stratified and blocked randomization will be performed. After providing written-informed consent and completing their baseline interview, participants will be randomized to one of two arms*:* 1) yoga-based intervention (YOGA)*;* or 2) a structured exercise program (SEP). ***The randomization process will be directed by Zhangsheng Yu, PhD (statistician) using statistical software with a random-number generator to create a list of group assignments before study recruitment begins. Randomization will be stratified by sex (men vs. women) and study recruitment site (VAMC vs. CBOC). Within strata, randomization with block sizes of 4 or 6 will be executed to ensure balance. Once an eligible participant has been screened, has signed informed consent, and has completed the baseline measures the research assistant (Amanda Gerwig) or project coordinator (Christy Sargent) will submit a request to randomize the eligible participant. The randomization program locates the first unassigned record in the randomization list and assigns the participant to the group designated in that record. The participant identifier and date are written to the record. To ensure allocation concealment, only Ms. Sargent and Dr. Bair will have access to the randomization table, but will not conduct outcome assessments. Dr. Yu will remain blinded to group assignment. No one will be allowed access to the folder of the randomization assignment until all baseline measures have been completed.***

D7. POYSE INTERVENTION DETAILS

The POYSE interventions will last 3 months. The length of follow-up and schedule of outcome assessments at ***1, 3, 6, and 9 months*** after the date of the first intervention session are to detect ***three*** types of treatment effects: 1) ***"early response" (at 1 month)***; 2) immediate post-intervention benefits at 3 months; and 3) sustained benefits at 6 and 9 months post-randomization (3 and 6 months post-intervention).

D7a. Overview of Yoga-based intervention

The yoga intervention **(Appendix 1)** will consist of three treatment components: 1) in-person group yoga sessions taught by a yoga therapist; 2) a relaxation audio recording for home-use; and 3) a DVD recording to reinforce concepts taught during in-person yoga sessions. The yoga intervention will complement standard medical treatments for fibromyalgia. It will involve 12 weekly group sessions of 8-12 patients per group. Each yoga session will last approximately 90 minutes and will be led by Nancy Schalk, Yoga Therapist (YT), who has over 30 years of experience in teaching yoga and meditation techniques to the general public and medical patients, including veterans. Ms. Schalk has trained in several schools of yoga, but draws most significantly from the *Sivananda* tradition. She has also received veteran-specific yoga training in a program called "Warriors at Ease." Ms. Schalk will be the lead yoga therapist, but will train and supervise other yoga therapists to enhance future implementation.

The yoga intervention is designed to improve functioning, pain, fatigue, sleep problems, and psychological distress common to patients with fibromyalgia. The intervention will include exercises or physical activity that includes postures (*asanas*), diaphragmatic breathing (*pranayama*), relaxation/meditation practices (*dhyanas*), and discussions sessions between Ms. Schalk and group

participants to exchange “lessons learned.” Patients will be given yoga mats and eye pillows and will have access to yoga blankets, yoga straps, and bolsters for doing yoga poses.

To standardize delivery and facilitate reproducibility of the yoga intervention, we detail the content and general structure of each class **(Table 2)** which will be followed by Ms. Schalk, YT. Procedures to assure *fidelity* to the yoga intervention will be used similar to those employed in our other trials. Briefly, steps will include: (1) extensive yoga therapist training conducted by Ms. Schalk during start-up; (2) observation of Ms. Schalk administering yoga sessions for at least one full wave (12 sessions) feedback provided by Ms. Schalk after review of several sessions and periodic meetings to discuss fidelity.

D7b. Yoga intervention site, schedule of sessions, and group size

The in-person group yoga sessions will be held at the Rehabilitation and Integrative Therapy Lab (RIT Lab, in Coleman Hall on the Indiana University Purdue University Indianapolis campus, School of Health and Rehabilitation Sciences. The RIT lab is less than a 10 minute walk from the RVAMC. The 12 weekly sessions will include 8 to 12 participants; a group size we found optimal during our pilot study.[72] Based on our sample size calculation, we will conduct 15-19 groups (of 8-12participants) to complete the yoga intervention. ***Attendance will be recorded to assess adherence to yoga.***

D7c. Yoga intervention components, sequence, and progression

The 12-week yoga intervention **(Table 2)** developed and previously tested by Drs. Schmid and Van Puymbroeck and Ms. Schalk[72] will be modified for veterans with fibromyalgia. For example, Ms. Schalk will emphasize “gentle practice” of yoga exercise when veterans are challenged by fibromyalgia or other chronic illnesses. The yoga exercises will be delivered in a standardized sequence and progression, as delivered in our pilot study of veterans with stroke. The yoga poses or *asanas* will consist of a single sequence that can be performed supine, seated, on hands and knees, prone, and standing. Similar to other rehabilitation interventions, our yoga intervention will progressively become more challenging for participants over the 12 weeks.

The standardized sequence of yoga poses will be introduced to participants. **Appendix 2** outlines the full array of poses to be used. The poses will begin in the seated position and consist of five poses that involve “breathing with movement” (head moves, scapula, and directions of the spine, pinwheel and pendulum). Additional poses will include: “table,” “cat cow,” “sunbird,” “downward dog,” “cobra,” “locust,” and “bridge.” Ms. Schalk will encourage the safe performance of physical poses and tailor them to participants’ needs and abilities. For patients with fibromyalgia, poses will avoid the extremes of range of motion. All sessions will end with a yoga *nidra (“yogic sleep”)* exercise to develop both deep relaxation and full alertness.

Deep breathing exercises will be taught and emphasized throughout every session. “Connecting with the breath” is a common theme in yoga and is combined with the poses (“breathing with movement”) to facilitate yoga practice. An effective breathing technique (alternate nostril breathing) will be taught to participants. All yoga sessions will include at least 10 minutes of relaxation, using progressive relaxation techniques. The relaxation component will be completed lying supine and aided with an eye pillow and yoga mat for each participant. The relaxation is based on resting the “physical body.”

Participants will be encouraged to exercise according to their limits, rather than rigid adherence to posture techniques. The yoga intervention will be tailored to the individual. It will include low intensity, low impact modified poses adapted with pathophysiologic changes of fibromyalgia in mind.[82] For example, and repetitive muscle movements will be minimized to reduce the potential for muscle micro-trauma theorized to occur in fibromyalgia patients. In addition, Ms. Schalk will encourage slow transitions from lying to standing to minimize dizziness and lightheadedness related to autonomic nervous system changes associated with fibromyalgia. Peripheral pain generators such as knee osteoarthritis, back pain, and carpal tunnel symptoms will be minimized by adapting standing poses to sitting or lying poses or using bolsters or pads. Previous studies that involved high intensity, repetitive exercises reported high rates of attrition or worsening fibromyalgia symptoms.[62, 82, 83] Tailoring of poses in POYSE is expected to yield lower attrition rates.

A proposed detailed schedule of the 12 yoga sessions and each session's content is found in Append

D7d. Yoga intervention: relaxation audio recording

From our pilot work, a relaxation audio recording was professionally developed and produced for participants. The recording features Ms. Schalk guiding a physical body relaxation exercise and is placed onto Playaway devices (www.playaway.com); an inexpensive (~$20) portable audio player. The Playaway device only holds the guided relaxation exercise and cannot be recorded over. It is easy to use, has simple directions, and works with minimal buttons, i.e. 'power' and 'play'. All participants randomized to the yoga arm will be issued a Playaway device and will be asked to listen to it three times a week to reinforce in-person yoga session content. ***Because the device records and times whether or not the device is used, this feature will help assess adherence to the yoga intervention and home use.*** We will record the date and time in minutes that audio recording is used at each session. Use of yoga will be tracked for the entire 9 month study period. To minimize lost devices, they will be labeled with POYSE study name and contact information.

D7e. Yoga intervention: DVD recording

All participants in the yoga arm will receive a DVD and an illustrated handbook to complement the audio recording. Similar to our audio-recording, the DVD will be professionally developed and highlight Ms. Schalk moving from start to finish through the yoga intervention. These DVDs will be given to participants at the beginning of the intervention and help participants apply yoga practices to daily life during the intervention period. Participants will be encouraged to practice at home for 20 to 40 minutes daily, at least 3 days per week. ***For adherence monitoring, participants will track their use of the DVD and record time spent in yoga practice on a form*** **(Appendix 5)**. These forms will be collected during the weekly sessions. To boost retention and adherence, POYSE study personnel will contact veterans' who miss a session to problem-solve regarding attendance barriers and or to address home practice barriers (if average practice < 20 minutes per home session).

D7f. Overview of structured exercise program group sessions

The group exercise sessions will also be held at the RIT lab in Coleman Hall on campus. Participants will undergo a graded aerobic exercise program; the preferred exercise prescription to reduce the possibility of exercise-induced pain.[48, 84-86] The exercise program will start at a low intensity, last for a short period of time, with gradual increases in exercise intensity and duration. Participants will start exercising at a slow pace for 5 minutes to warm-up. For each 5-minute phase (total of 30 to 35 minutes total per session), the exercise intensity will be gradually increased to the mid-range of their exercise prescription.

During the first exercise session, the fitness instructor will provide an introduction and overview of the exercise program. Veterans will also receive instructions on how to use the heart rate monitor, pedometer, and how to rate their perceived exercise exertion according to the Borg scale. In addition, veterans will learn how to keep an activity diary at home and how to select physical activities and exercises based on heart rate, perceived exertion, or metabolic energy costs. Further, subjects will have their blood pressure and heart rate monitored during all sessions. Subjects will be asked to report any cardiovascular symptoms such as shortness of breath or chest pain while exercising. If a subject experiences any cardiovascular symptoms or an unsafe blood pressure or heart rate the instructor will cal an ambulance to transport the subject to the VA ER for immediate medical assessment.

Exercise sessions with other participants and the fitness instructor will last approximately 75 minutes and occur once a week for 12 weeks; the same session schedule and duration as the yoga arm. The fitness instructor will teach participants to use a table-top ergometer at a sub-maximal level, determine baseline fitness, and develop an individualized exercise prescription. The fitness instructor will provide educational tips on exercise and selection of physical activities. The instructions will be informed by veterans' heart rate (at baseline and at different exercise levels), their ratings of perceived exertion, and metabolic activity (METS). While we will employ individualized exercise prescriptions for veterans

randomized to the structured exercise program (SEP) arm, the SEP will be delivered in a group/class format to control for the potential benefits of social interactions and attention across treatment arms.

D7g. Exercise ergometer starting point, perceived exertion, and metabolic activity

In general, participants will start exercising with the ergometer at a power of 30 watts for 5 minutes, followed by increases of 15 watts every 5 minutes until veterans reach their sub-maximum target heart rate [(220 − age) × 0.85]. After each 5-minute phase, heart rate, blood pressure, and a rating of perceived exertion will be recorded. To obtain ratings of perceived exertion, veterans will be evaluated according to the Borg Scale,[87] which ranks exertion ordinally ("very, very light" to "very, very hard"). These terms are assigned a number from 7 to 20. If the target heart rate is not reached, the test will be stopped at a score of 17 ("very hard"). We want participants to exercise with the ergometer at a level associated with a perceived exertion of 12 on the Borg Scale, i.e. the level below "somewhat hard" for the prescribed duration while wearing a heart rate monitor. This level is consistent with light-to-moderate exercise recommended in the fibromyalgia literature.[48, 84-86]

Combining perceived exertion with the structured exercise program allows veterans to better gauge their "comfort zone" and select physical activities based on how they feel on any given day. Heart rate monitoring provides useful information for our fitness instructor and veterans to set their exercise intensity based on different levels of exercise. Energy output data from the sub-maximal test will be converted to equivalent energy costs in metabolic activity (METS). The METS will then be benchmarked for a wide variety of recreational and occupational activities relevant to the veteran.

D7h. Schedule and content of weekly exercise sessions

In addition to the schedule of supervised group exercise sessions as shown in Appendix B, veterans will be asked to exercise independently a minimum of two or three times per week during the 12-week intervention period. ***To track the extent of home exercise and activities***, ***we will ask participants to fill out and bring their tracking diary to each exercise session***. The exercise intensity will be modified during sessions according to how the veteran reacts to exercise. The intensity and duration of each exercise session will be gradually increased as tolerated and as the veteran's fitness level changes. At each weekly session, veterans will report the number of times and the total minutes exercised. The self-report of at home exercise activity will be confirmed with pedometer readings, i.e. step counts. After the 12 sessions are completed, study personnel will conduct monthly calls at months 4, 5, and 6 to ***check adherence***, prevent inactivity, and track exercise activity during the follow-up period.

After the first session, participants will receive a brief educational message each week from the fitness instructor. After soliciting what exercise activities veterans are willing to do, the fitness instructor will teach ways to incorporate physical activities in veterans' daily life. Participants will also learn their typical heart rate, rating of perceived energy, and metabolic energy cost associated with each activity and provide a record of their weekly activities using an activity diary and step count assessed from their pedometer. The importance of regular physical activity for improved health and adherence to the individualized exercise prescription will be emphasized at each session. For "homework", veterans will be asked to choose a physical activity to do before the next session. Educational messages will be reinforced with a professionally produced exercise DVD to view at home. The exercise DVD will contain instructions to modify participants' exercise in case of a flare of their fibromyalgia and to be progressive (chair work to standing) in terms of intensity and duration depending on their baseline exercise prescription. ***Attendance at the exercise group sessions will be recorded.***

D7i. Plans to manage exercise-induced pain and injury

Strenuous exercise, especially if done too vigorously, can exacerbate fibromyalgia symptoms and adversely affect exercise adherence.[88] Exercise-induced pain is postulated to be caused by an overload of local musculoskeletal structures, leading to micro-trauma or tendonitis[89-91] or to "central sensitization" (amplification of sensory processing within the brain)[92-95] resulting in an exacerbation of symptoms. Patients who suffer from exercise-induced pain often do not follow through with an exercise

program; consequently, affecting adherence and clinical outcomes. To improve adherence and clinical outcomes, exercise prescriptions should be individualized based on patient's baseline severity of pain and fatigue, and tolerance to exercise-induced pain.[82,88]

To minimize muscle micro-trauma and exercise-induced muscle soreness, we will employ the following safety precautions:

1. Participants will be advised not to exceed the prescribed exercise (frequency, intensity, or duration) during a "good day."
2. Participants will be forewarned that even exercise performed at the appropriate intensity might result in *short-term* increases in exercise-induced pain and fatigue that should dissipate within a few days (up to 2 weeks).
3. Participants will be allowed to self-adjust their exercise intensity, especially during a flare.
4. Participants who develop intolerable exercise-induced pain (or fatigue) will be instructed to avoid exercise for 48 hours, then restart the program at 5% below the previous exercise intensity (e.g., from 55% to 50%) for one week, and maintain the same exercise duration for one week, thereafter. Then resume the previous exercise intensity (e.g. 50% back up to 55%), and continue on with the original exercise prescription.
5. Should a participant develop an increase in regional body pain (e.g., foot or ankle pain) as a result of the aerobic exercise, they will be asked to do the following:
    a. **RICE**: Rest, Ice, Compression of injured tissue, and Elevation during the first 24 hours,
    b. Switch to a different type of exercise (e.g., from brisk walking to bicycling or from weight bearing to non-weight bearing exercise).
6. In the event that participants are unable to exercise for > 2 weeks, they will be instructed to resume their exercise at 65% of their previous exercise duration (in minutes) and 5% below the previous exercise intensity. If they fail to exercise for < 2 weeks, they will restart at the level (i.e. duration and intensity) from where they left. Then, they will follow the original recommendation of gradually increasing the exercise duration (in minutes) each week and the exercise intensity each month.

D7j. Co-interventions

Participants will continue to be followed by their treating physicians/providers for all medical care unrelated to the trial. This includes continuation of other medications as prescribed, clinic visits, and other care as usual. Specifically, use of medications, and specialist consultations (rehabilitation, pain management, and rheumatology) for fibromyalgia will be permitted (and assessed), both to adjust for co-intervention differences between arms in the analyses and to assess as secondary outcomes.

D8. DATA COLLECTION PROTOCOL

The schedule of outcomes and key variables to evaluate the effectiveness of the POYSE interventions are listed in **Table 3**. After obtaining informed consent **(Appendix 3)**, a research assistant will administer a baseline assessment to gather socio-demographic data, body mass index, review the patient's history emphasizing previous treatments tried for their fibromyalgia, and administer several validated measures to assess fibromyalgia related symptoms, function, pain, and psychological status. The data collection protocol is informed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) recommendations,[97] biopsychosocial conceptual model,[79] and our previous studies.[66,98]

To minimize the potential for ascertainment bias, the baseline and follow-up assessments will be conducted by a research assistant blinded to treatment assignment. The baseline interview will take approximately *45 minutes*, the 1, 3, *6, and 9 month* interviews about *30 minutes*. These assessments will be completed by our research assistant and generally conducted in-person, unless telephone interviews are preferred for veteran convenience. We have found that face-to-face interviews are more effective in establishing rapport. Additionally, we have found phone interviews over 30 minutes to be burdensome to both patients and interviewers. We have used a battery of measures of similar length in

several previous or current trials without over-burdening patients. All measures have been conducted both in person and by phone in multiple prior trials. Both types of administration have routinely been approved by both Indiana University IRB and VA Scientific Review Committee.

If participants cannot be scheduled for an in-person interview or reached by phone we have employed two strategies to capture all outcome assessments: (1) send a mailed questionnaire to the veteran with postage paid, self-addressed envelope to our office; and 2) conduct a face-to-face interview in conjunction with the patient's clinic visit. Veterans occasionally lack transportation to the in-person interviews. In this situation, we have previously arranged taxi cab rides to and from our VA.

To protect against data loss, participant responses are collected in two formats: paper and electronic. The interviews and study databases will be designed in Microsoft Access by Mr. Jeff Barnd, MS, one of our Center's data managers. To maintain confidentiality of veterans interviewed, our research assistant will adhere to careful interview and data collection procedures. First, participants will be told that their responses will remain confidential and that every effort will be made to fulfill that assurance. Second, the interviews will be conducted in an appropriate setting (i.e., private interview room). Third, completed surveys will be stored in a secure location in our Center in a locked file cabinet.

D8a. Primary Outcome Measure

The primary outcome measure will be the **Total Score** from the **Fibromyalgia Impact Questionnaire Revised (FIQR)**. The FIQR **(Appendix 4)** has been found to be a useful brief instrument to assess the overall impact and severity of fibromyalgia.[99] The FIQR is an updated version of the widely used Fibromyalgia Impact Questionnaire (FIQ) which has been extensively used and validated in clinical trials. The FIQR consists of 21-items that assess pain, fatigue, stiffness, sleep, depression, memory, anxiety, balance, and environment sensitivity.[9,99] All items are framed in the the past 7 days and are scored on an 11-point numeric rating scores of 0 to 10, with 10 being "worst." The total score range from 0 to 100, with higher scores representing greater symptom burden and functional limitations from fibromyalgia. The FIQR has strong internal consistency (Cronbach's alpha = 0.79 to 0.93) and is comparable to the original FIQ allowing comparisons between the FIQ and FIQR.[100] In addition to the Total Score, the FIQR contains scales for Symptoms (10 items), Function (9 items), and Overall Impact (2 items); the most important domains in fibromyalgia trials. Scoring of the FIQR involves: 1) summing the score for function (range 0 to 90) and dividing by 3; 2) summing the score for overall impact (range 0 to 20); and 3) summing the score for symptoms (range 0 to 100) and diving by 2. The three domains are weighted; 30% of total score ascribed to function, 50% to symptoms; and 20% for overall impact.

D8b. Measures, Schedule, and Mode of Administration

In addition to our main outcome measure (FIQR Total Score), we will also measure several other secondary outcomes recommended by the OMERACT guidelines[97,101] and consonant with the biopsychosocial model at each follow-up assessment. These include depression, anxiety, health related quality of life, pain beliefs, fatigue, sleep, and self-efficacy. These variables are important to assess as key moderators or mediators of intervention effects. Finally, measures of fitness and physical activity as well as measures of ***satisfaction and adherence to the interventions*** will be assessed. We will also assess the performance of all scales to ensure they meet standard psychometric characteristics.

Baseline patient characteristics will be evaluated with an interview adapted from our previous pain and fibromyalgia trials and will include socio-demographics, disability compensation, comorbid medical and psychiatric disorders, and prior treatments for fibromyalgia. We will also regularly assess use of other treatments for fibromyalgia (other medications, exercise, physical therapy, complementary and alternative medicine modalities, and interventional modalities) as well as prescription medication use. For medications, we will record prescribed doses, administration schedule, and number of pills prescribed, especially opioid analgesics, antidepressants, and benzodiazepines.

D8c. Description of Specific Measures

Fibromyalgia symptom severity will be assessed with the Fibromyalgia Impact Questionnaire Revised (FIQR).[9]

Pain-severity: The Brief Pain Inventory is an 11-item, multidimensional pain measurement tool with demonstrated reliability in patients with arthritis as well as other pain conditions.[102,103] The BPI rates the intensity of pain as well as the interference of pain with mood, physical activity, work, social activity, relations with others, sleep, and enjoyment of life.

Psychological symptoms are frequently associated with fibromyalgia and will be assessed by:

The PHQ-9 will be used to assess depression severity. Several studies have validated the PHQ-9 as a diagnostic measure with excellent psychometric properties.[104] Internal consistency has consistently been shown to be high (Cronbach's alpha > 0.80) and test-retest assessment showed the PHQ-9 to be a responsive and reliable measure of depression treatment outcomes.

The GAD-7 has demonstrated reliability (alpha = 0.89) and validity (criterion, construct, factorial, and procedural) as a measure of anxiety in the general population and primary care.[105]

The Primary Care PTSD Screen (PC-PTSD) has been validated for use in VA primary care settings.[106] The sum of the 4 yes/no items yields a score ranging from 0 to 4, with scores ≥ 3 considered positive for active PTSD. Sensitivity is 78% and specificity is 87% compared to clinician interview.[107] In participants who screen positive, the PTSD Checklist for Military (PCL-17) will be administered. This 17-item scale assesses the DSM-IV symptoms of PTSD, and is used for diagnosis and as a severity measure as a measure of change in PTSD symptoms as a function of treatment. The PCL has demonstrated sensitivity and specificity >70%.[107]

Table . Outcome Assessment Protocol: Measures and Schedule of Administration

Domain	Measure	Items	Time (min)	Schedule				
				BL	1 mo	3 mo	6 mo	9 mo
Covariates	Demographics; contact information; disability compensation, comorbidity; pain treatments	36	10	X				
Fibromyalgia severity	Fibromyalgia Impact Questionnaire Revised	21	6	X	X	X	X	X
Pain Severity	Brief Pain Inventory	10	3	X	X	X	X	X
Psychological	PHQ-9 Depression	9	2	X		X		X
	GAD-7 Anxiety	7	2	X		X		X
	VA PTSD Screener	4	1	X		X		X
	VA PTSD Checklist (PCL-17)	17	4	X		X		X
Generic HRQL	Medical Outcomes SF-12	12	4	X		X		X
Fatigue	Multidimensional Fatigue Inventory	20	5	X	X	X		X
Sleep	MOS Sleep Scale	12	3	X	X	X		X

Pain beliefs	Pain Catastrophizing Scale	10	3	X		X		X
Pain coping	Centrality of Pain Scale	10	3	X		X		X
Self-efficacy	Arthritis Self Efficacy Scale	6	2	X		X		X
Treatment Response	Global Rating of Change	1	1		X	X	X	X
Physical Function and Activity	Functional Assessment which includes Fullerton Advanced Balance Scale (FAB)	18	10	X		X	X	
	Rapid Assessment of Physical Activity	8	2	X		X		X
	Activity Constraints	20	5	X		X		X
	Activities - Specific Balance Confidence Scale (ABC)	16	5	X		X		X
	Balance	7	2	X	X	X	X	X
Coherence	Sense of Coherence Scale	3	1	X		X		X
Substance Use	Illicit use and personal/family history	6	2	X				
Perceived Expectations	EXPECT Questionnaire	26	8	X	X			

Other secondary outcome measures and potential predictors of treatment response will be assessed**:**

The Medical Outcomes Study Short Form Questionnaire (SF-12) is the criterion standard for generic functional status and health-related quality of life.[108] The SF-12 assesses physical and mental functioning in 8 domains and gives reliable, valid and responsive summary scores.[108]

The Multidimensional Fatigue Inventory (MFI) will be used to assess fatigue.[109] The MFI assesses clinical fatigue in 5 dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. The MFI has been validated among adults with chronic illness, chronic fatigue syndrome, and cancer, as well as among healthy adults.[110]

Sleep problems will be assessed using the MOS Sleep Scale which assesses sleep disturbance, adequacy of sleep, and sleep quantity. The MOS-Sleep Scale has demonstrated good psychometric properties in trials assessing pain.[111]

The Pain Catastrophizing Scale a 13-item scale that assesses catastrophizing—a pain belief that has been found to be strong predictor of poor treatment response.[112] Validation studies examining the PCS have found strong evidence of criterion-related, concurrent, and discriminant validity.[112]

The Centrality of Pain Scale is a 10-item measure to measure how central chronic pain is to a patient's life.

The Arthritis Self-Efficacy Scale will be used to assess self-efficacy.[113] This 8-item scale proved sensitive to change in our low back pain trial.[114] For each item, patients report their degree of certainty on a scale ranging from 1 (very uncertain) to 10 (very certain).

The Patient Global Impression of Change (PGIC) is a single item measure to assess overall clinical response. This validated and reliable global rating scale is often used as the gold standard for determining clinically important differences in outcomes[115,116] and required by the Federal Drug Administration in fibromyalgia trials. The PGIC asks subjects to rate overall improvement in symptoms using a single 7-point scale anchored by "very much improved" and "very much worsened".

The Rapid Assessment of Physical Acitivity (RAPA) is a 7 item measure of physical activity for use with older adults.

The Activity Constraints is a 20-item measure which assessing seven different types of constraints on a 5-point Likert scale.

The Activities – Specific Balance Confidence Scale is a 16-item scale to assess a subject's balance confidence in performing several activities.

The SOC-3 (3-item Sense of Coherence scale) will be used to measure the 3 dimensions salient to resilience and coherence including manageability, meaningfulness and comprehensibility.

Substance use problems will be assessed by asking questions about the use of others' prescription drugs or street drugs.

The EXPECT Questionnaire is a 26-item measure assessing the perceived expectations of the subject for the intervention.

A Functional Assessment will consist of monitoring blood pressure, pulse, six minute walk, gait analysis, chair sit and reach test, back scratch test, chair stand test and the Fullerton Advanced Balance Scale.

Health Care Utilization and Costs: will be assessed at the end of the 9 month study period for each patient using data available in CPRS. This will include all outpatient, rehabilitation, and emergency room visits, inpatient days, x-ray and lab tests, medical and surgical consultations, and medications.

D9. STATISTICAL CONSIDERATIONS

POYSE will involve a 2-arm, parallel group, randomized comparative effectiveness trial. Since participants cannot be blinded to treatment assignment, observed outcomes (if positive) could be affected by expectation bias. To account for this potential bias, we will assess treatment expectations at baseline and account for expectations in our analyses. We will randomize at the patient rather than the provider level for two reasons: (1) randomization at patient level saves sample size; and (2) patients from the same provider in the two arms will adjust for "provider effect." Contamination will also be low because there is relatively minimal involvement required of VA providers in POYSE. In addition, randomization will be stratified by sex (women or men) and ***study recruitment site (VAMC or CBOC)*** to avoid potential imbalance of these factors between the two arms. Dr. Yu, PhD (statistician) will create a randomization chart to randomize patients in ***blocks of 4 or 6***.

D9a. Sample size

Our sample size is calculated based on estimated differences of intervention effects between two arms on the primary outcome; Fibromyalgia Impact Questionnaire Revised (FIQR) total score at 3 months. The FIQR total score is a continuous measure: a 0-100 scale and reflects the average of three domains: function, overall impact, and symptoms. In a recently published yoga trial for patients with fibromyalgia, Carson et al.[61] found a pre-treatment FIQR score of 48.3 (standard deviation = 17.5). Post-treatment scores were reduced by 31% (FIQR = 35.5, SD = 17.6, effect size = 0.72) from the yoga intervention. In an earlier trial, Mannerkopi et al.[118] tested an intervention combining pool exercises with

cognitive behavioral relaxation techniques and found a 13.6% reduction in FIQR scores. From these studies, we estimate the difference between the yoga and structured exercise group is 17%. A between-group treatment difference of 14% reduction in symptoms represents a minimum clinically meaningful intervention effect.[119] To be conservative, we will assume a 14% difference between treatment groups. The absolute score difference at 3 months is estimated to be approximately 7 points (6.79, 14% of 48.3). Assuming a common standard deviation of 17.6 and using a two-sample t-test, we will need 107 evaluable subjects in each arm to detect such a difference with >80% power and 5% Type I standard error rate.

We recognize the correlation of outcomes from subjects within the same yoga or exercise class may reduce the effective sample size compared to the same sample with independent observations. This possible "clustering effect" seen in group delivered interventions has implications for power. We have no preliminary data to estimate the intra-cluster correlation (ICC) for participants within the same group. However, based on similarly designed published studies, we expect the ICC to be relatively small and balanced across the two treatment arms since the cluster sizes will be similar.[120] Conservatively, we assume an ICC of 0.02 for both treatment groups. With 8 subjects per treatment group/class or cluster, the design effect is 1+ (8-1) ×0.02 =1.14. Therefore, we will inflate our sample size by 14% to accommodate the potential clustering effects. We then need 122 evaluable subjects in each arm. With a conservative 20% attrition, we will then need (122*2)/0.80 = 306 subjects (153 in each arm).

D9b. Data analysis: Baseline characteristics of POYSE sample

We will examine baseline characteristics (socio-demographic variables, medical and psychiatric comorbidity, duration of fibromyalgia, and current and prior pain treatments) of the POYSE sample. To evaluate the representativeness of study enrollees among all eligible patients, we will compare the enrollees and those who decline enrollment on their demographic characteristics. If there are systematic differences, these will be considered in the interpretation of the results of subsequent analyses. We will also examine differences in baseline characteristics between patients who remain in the study and those who dropout. Two-factor ANOVA models which include dropout status, treatment group (YOGA vs. SEP) and their interaction will be used for continuous variables. Logistic regression models with the same terms will be used for dichotomous variables.

D9c. Main analysis of the primary outcome (FIQR total score)

Our main analysis will employ a repeated measurement analysis of covariance (ANCOVA) model which is more powerful than two-sample t-test when the baseline outcome measurement is positively correlated with post baseline outcome.[121] We plan an intent-to-treat analysis approach with the primary endpoint at 3 months and evaluation of "early" response at 1 month and "sustained" response at 3 and 6 months post-intervention. We will summarize this primary outcome at each time point (baseline, 1, 3, 6, and 9 months) for both arms. The difference between time points will be compared.

Since the primary outcome (FIQR total score) is measured repeatedly at baseline, 1, 3, 6, and 9 months, we will fit a repeated measurement analysis of covariance (ANCOVA) model with the four post baseline (1, 3, 6, and 9 months) FIQR total score as the response variables. The main predictors will be group (treatment arm), time (categorical), and their interaction. The model will be adjusted for baseline FIQR score. A random intercept will be used to adjust for the patient effect and to accommodate the correlation among the repeated measurements from the same patients. Another random intercept will be used to adjust for the potential clustering effect for patients in a specific yoga or exercise group. The primary analysis will evaluate the difference in FIQR score between the two treatment arms at 3-months (the primary end point) using appropriate contrast in this model. The sustained effect of intervention will be evaluated using appropriate contrast for the difference in FIQR change from 3-month to 6-month in this model.

D9d. Secondary analysis of primary outcome

For the FIQR total score, we will also define the patients with more than 30% reduction as "responders." We will then compare the probability of responders between treatment arms using a generalized linear mixed model with a logit link. The responding status of each patient at ***1, 3, 6, and 9 months*** will be used as the outcome variables. Main predictors are group (treatment arm), time (1, 3, 6, and 9 months), and their interaction. A significant coefficient of group indicates a significant odds ratio of being a responder between the two arms at each time point. Each of the three domains of the FIQR score will be analyzed in the similar way to the total score.

D9e. Analysis of secondary outcomes

Since POYSE is not specifically powered for the secondary outcome, these results should be interpreted cautiously unless they are highly significant ($p < .001$). Pain severity as assessed by the Brief Pain Inventory will be analyzed using a repeated measurement ANCOVA model in the same way as the FIQR total score. BPI measurement at 1, 3, 6, and 9 months will be used as the response variable. Main predictors will be intervention group, time (categorical), and their interaction adjusted for the baseline BPI score. A random intercept of subject effect will be used to accommodate correlation within subject. Another random intercept of either a specific yoga or exercise group will be used to accommodate correlation within group (clustering effect for group delivered intervention).

Psychological symptoms: PHQ-9 score, GAD-7 will be analyzed using a repeated measurement ANCOVA model in the same way as the FIQR total score with repeated outcomes at 1, 3, 6, and 9 months as the response variables, the same set of main predictors and adjusted for baseline outcome measurement. The PTSD screening status will be analyzed using a generalized linear mixed model with a logit link. The main predictors will be intervention group, time (categorical) and their interaction adjusted for baseline PTSD screening status. PTSD severity from PTSD checklist for military will be analyzed similarly.

Other secondary outcome measures: The analytical strategy for other outcomes will be similar to the FIQR total score. These outcomes include SF-36, MFI, MOS Sleep Scale, Pain Catastrophizing Scale, Arthritis Self-Efficacy Scale, and PGIC.

We will employ several secondary analyses to assess the effectiveness of the treatment arms compared to each other in improving:

- Individual fibromyalgia symptoms (pain, fatigue, sleep quality, function)
- Health-related quality of life
- Patient global impression of change
- Pain beliefs and self-efficacy

Analytic techniques will be similar to those previously described. Since there will be a number of secondary outcomes, we will account for multiple-comparisons in analyses. We will use the Bonferroni approach to adjust for statistical significance threshold when the number of tests is less than 20. Otherwise, we will use the false discovery rate (FDR)[122] to control the magnitude of false positives. We will also stratify our analysis based on a baseline depression status (PHQ-9). Our previous research indicated that 30% to 40% of patients will have clinically significant depression, which may adversely affect pain outcomes. Thus, depression is a potential moderator.

D9f. Missing data

Missing data are unavoidable in longitudinal studies. Based on our prior studies, we anticipate a possible dropout rate between 8% and 12%. However, we conservatively estimated a possible 20% drop out rate which is reflected in the sample size calculation. We will first run a logistic model with missing status as the response variable, intervention arm, patients' demographic characteristics as covariates to check whether the missing status depends on the intervention group assignment and patient characteristics. Second, our linear mixed-effect model can accommodate missing-at-random (or

MAR which is assumed in many trials)[123] where no bias will be introduced by ignoring the missing-data mechanism. If drop-outs are Missing Not At Random (MNAR), meaning the likelihood of drop-out depends on an un-observed outcome, and the missing data mechanism is ignored, potential bias can be introduced. We will run sensitivity analyses using complete cases, last observation carried forward imputation, other multiple imputation methods including linear mixed-effect model, to compare results across these analyses to assess the robustness of the inference.

D9g. Economic evaluation

We will conduct cost effectiveness to determine if changes in health care utilization may offset the intervention costs between treatment arms. To conduct this analysis, we will use established methods[124] to estimate direct costs of the interventions and health care spending for study participants during the ***9 month*** trial period from the perspective of the VA.

D9h. Costing

We will use both micro- and gross (average) costing methods[125,126] to estimate intervention and health care utilization costs, respectively. Applying VA Health Economics Resource Center (HERC) guidelines, we will measure intervention-related activities and their associated costs.[125] These intervention costs will include: 1) yoga and fitness instructor average salaries plus fringe benefits; 2) study materials (yoga mats, eye pillows, DVDs, audio-recordings, ergometers, heart monitors, pedometers) provided to intervention patients; 3) parking; and 4) facility overhead.

We will use VA DSS data to obtain health care utilization and cost estimates for trial participants. From the VA Patient Treatment File (PTF), we will collect hospital discharge date, days of hospital stay, and ICD-9 diagnoses (especially primary or secondary diagnoses) of fibromyalgia for each stay and determine the cost per admission. From the Outpatient Care File (OPC), we will collect dates of any outpatient visits for fibromyalgia, location of care (stop code), CPT codes assigned to each visit, and type of provider delivering care. We will classify all visits into rehabilitation, primary care, emergency, pain, specialty medicine or surgery, mental health, and other treatments based on clinic codes.

The number of outpatient prescriptions, especially for analgesic and psychotropic medications, will be found in the DSS NDE Pharmacy Datasets from VA Information Resource Center (VIReC).[127] Laboratory and x-ray testing will be collected to determine the number of tests for fibromyalgia evaluation and the costs per test. The cost of other care will be obtained from utilization data included in VA Austin databases. For non-VA care, covered by the VA, fee basis files will be merged into DSS data.[128] For non-VA care not covered by the VA, we will we rely on patient self-report of outpatient visits and hospitalizations. Since VA utilization data does not include cost estimates, the above mentioned data sets will be merged to the HERC average cost datasets to estimate the costs associated with VA utilization for each participant.[129,130]

D9i. Analysis

To estimate cost effectiveness, the dependent variable will consist of primary cost outcomes calculated from the VA health care system perspective. Having obtained the relevant VA healthcare utilization events, the healthcare event requires valuation, which is the task of assigning a reasonable market-level dollar for the expense amount. For each patient, outpatient events (visits, procedures, labs, medications, etc.) and inpatient DRGs and medical events (procedures, labs, medications, etc.) will be captured from these patient-specific administrative datasets. VHA databases provide sufficient outpatient and inpatient procedure and associated treatment classifications (by CPT-4, DRG and ICD-9 codes) to allow valuation. Dr. French has created similar datasets in other VA funded studies and publications. For health care utilization and the associated costs, we will compare inpatient days, outpatient visits, telephone care, number of prescriptions and radiographic tests. However, we may not be able to include inpatient costs because hospitalization may occur rarely during the 9 months of the trial and make estimates of between-group differences imprecise.

We will compare the two treatment arms with respect to total health care costs. Univariate, bivariate and regression techniques for repeated measures will be used to estimate the healthcare events and expenditure amounts. If cost data are skewed, log transformations will be performed prior to performing regression. An ANCOVA model will be used and contain treatment group (independent variable) and adjusted for comorbidities, age, and previous health care cost data collected at baseline as a covariate.

Costs will be reported in current year's dollars. Sensitivity analyses will be used to account for assumptions, including changes in intervention costs and changes in costs related to inpatient or outpatient services. If the interventions are found to be differentially more effective and costly, we will perform a cost-outcome analysis (i.e., incremental cost-effectiveness). We will estimate the effect of the interventions on the primary outcome (FIQR total score). The incremental cost to achieve a clinically meaningful decrease in FIQR total scores due to the interventions, i.e., the cost-effectiveness ratio, is calculated as the difference in intervention costs between the two treatment arms, divided by the difference in effectiveness between groups.

$$\frac{\text{Intervention Costs} + (\Delta \text{ Health Care Costs})}{(\Delta \text{ FIQR}_{\text{Yoga}}) - (\Delta \text{ FIQR}_{\text{Structured Exercise Program}})}$$

Where Δ FIQR = change in FIQR score, and Δ Health care costs = difference two groups

D10. PROJECT MANAGEMENT PLAN

D10a. Project Timeline

The 1st quarter in year 1 will involve hiring and training personnel. Important steps will include: (1) finalizing treatment protocols for yoga and exercise arms; (2) training the research assistant in screening, enrolling, and consenting study participants; (3) programming the electronic medical records to identify potential study subjects based on fibromyalgia diagnosis; and (4) obtaining permission from individual treating physicians to approach patients of theirs who might be eligible. During the next 2.5 years, we will enroll ***306*** participants (randomizing ***153*** to each group). Enrollment will average 10 per month. The ***306*** participants will be treated for 3 months. Participants will have outcome assessments at baseline, ***1, 3, 6, and 9 months***. Thus, enrollment will be conducted from the 2nd quarter (year 1) until the 4th quarter (year 3); the intervention phase from 2nd quarter (year 1) until 1st quarter (year 4); and outcome assessments from 2nd quarter (year 1) until the end of study period. Baseline analysis will begin at the beginning of year 4 and conducted during the final 9 months of the study (separate baseline, 3 month, and end-of-study analyses). Main reports and manuscripts will be prepared in the 3rd and 4th quarters of Year 4.

POYSE Study Timeline

	Year 1				Year 2				Year 3				Year 4			
Quarters	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Start-up																
Enrollment																
Intervention																
Assessments																
Analysis																
Manuscripts																

D10b. Overall project coordination and facilities

Overall project coordination will be led by Dr. Bair (PI) and Ms. Sargent (Project coordinator). Ms. Sargent will coordinate all aspects of the project, trouble-shoot any problems, and provide regular updates on recruitment progress. Drs. Bair, Schmid, and French have office, meeting and research space within the HSR&D Center for Implementing Evidence-based Practice (CIEBP) at the RVAMC. Dr. Ang and Dr. Yu's offices are a 5-minute walk or drive, respectively from CIEBP. Dr. Van Puymbroeck will be available for the monthly study-related teleconferences.

D10c. Investigator roles

The proposed project will be conducted by a strong multidisciplinary team with extensive experience in areas relevant to this study. Specific roles of the research team are outlined in more detail in the budget justification. The efforts of each of the investigators will be coordinated by Dr. Bair and Ms. Sargent to develop plans, review progress, discuss analysis results, and set priorities for the research team. Matthew Bair, MD, MS, has expertise in pain interventions in primary care and chronic pain and depression comorbidity. He will serve as PI and provide overall study direction. Dennis Ang, MD, MPH, is a rheumatologist-investigator with expertise in fibromyalgia clinical and translational research. He will serve as the study's clinical content expert. Arlene Schmid, PhD, OTR is an occupational therapist-investigator and will contribute her expertise in developing and testing yoga interventions in veterans and relevant rehabilitation outcomes. Marieke Van Puymbroeck, PhD, CTRS, is a rehabilitation scientist and recreational therapist with extensive yoga research experience. She will assist in ensuring fidelity and excellent quality of yoga therapy. Kristine K. Miller, PT, MS is a physical therapist and will train and supervise our fitness instructors in delivering the structured exercise program. Dustin French, PhD, is a health economist-investigator with extensive experience in VA large database research. Dr. French will guide the economic analysis. Zhangsheng Yu, PhD, is an experienced clinical trial biostatistician who will lead the data analysis. Additional analytic support will be provided by James Slaven, MS, who specializes in hierarchical and longitudinal analyses. Nancy Schalk, YT will deliver the yoga intervention. Christy Sargent, BA, will serve as project coordinator, Amanda Gerwig, BS as the research assistant, and Jeff Barnd, MS as the data manager.

D10d. Data Management

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

D10e. Data Safety Monitoring Plan

The following multi-component Data Safety Monitoring Plan has been used in our VA RR&D-funded ESCAPE trial of OEF/OIF veterans with chronic musculoskeletal pain and NIMH-funded pain/depression SCAMP trial. Subjects are monitored during study interventions in the following ways: 1) frequent subject contacts by research team members. Responses to the interventions, as well as side effects from them are closely monitored. All interview responses are part of the study database. 2) Monthly Executive Committee Meetings. The PI and co-investigators meet monthly for Executive Committee meetings. At these meetings the investigators discuss recruitment, subject safety, protocol adherence, and any other issues that may arise. Minutes are kept and are circulated to any co-investigators not able to attend. Subjects will be allowed to withdraw from the trial at any time. If a patient withdraws, we will determine the reason for withdrawal. Possible reasons will include: 1) death, 2) worsening of comorbid medical conditions making follow-up impossible, 3) treatment side effects, and 4) other. If subjects withdraw, we will attempt to obtain their permission to complete the remaining

outcome assessments. We will establish a local Data Safety Monitoring Board (DSMB) that meets every 6 months during the study and is notified via email of all deaths and SAEs at the time of local IRB notification. Members will consist of non-study investigators and will include a pain specialist, a rheumatologist, a clinical trialist, a nurse, and a biostatistician.

The DSMB will monitor the following: (a) subject recruitment, accrual, and retention; (b) patient outcomes and adverse events; (c) subject safety, privacy, and confidentiality procedures; (d) diversity of subject enrollment (i.e., sex and race); (e) data quality and major findings in terms of treatment benefits and risks; (f) results of related studies that impact subject safety; (g) assessment of scientific reports that might alter the benefit/risk ratio of the study. Analyses of data will be performed by the study biostatistician but will be independently interpreted by the DSMB (which will include an independent biostatistician) which can request additional analyses as the DSMB members see fit. Since this is an effectiveness trial using evidence-based treatments, there are no pre-planned interim analyses or stopping rules. The DSMB will submit the report of its annual meeting to the study investigators who will in turn report the information to IRB in its continuing review, unless there are items DSMB feels should be reported to IRB immediately.

D11. DISSEMINATION AND IMPLEMENTATION PLAN

The VHA National Pain Management Strategy Coordinating Committee will serve as our primary channel for disseminating study findings to VA providers, administrators, researchers and policy makers. Findings will be disseminated to the committee in the form of summary reports and presentations given either in the monthly conference calls or at their annual face-to-face meeting (or both). The Committee will advise and coordinate next steps for dissemination, including dissemination to other relevant entities such as VISN and hospital administrators; local Pain Management Committees; the VISN Pain Points of Contact, the Office of Quality and Performance; and the national working groups related to pain management education, guideline development, and performance measures. Additionally, a summary of study findings and implications will be posted on the VHA Pain Management Committee's website in a format readable to veterans. Findings will be disseminated to our research audiences through scientific presentations and publications, and VA cyber seminars, as well as through conference calls with the Pain Research Working Group, a subcommittee of the VHA National Pain Management Strategy Coordinating Committee.

We also will seek synergistic opportunities with the Pain Research, Informatics, Medical comorbidities and Education (PRIME) Center directed by Dr. Robert Kerns (VA National Program Director for Pain Management). Other resources include a VA national pain management website; a widely subscribed VA pain list serve; monthly national educational teleconferences targeting providers and administrators; a network of VISN Pain Points of Contact who hold monthly teleconferences and who serve an important liaison role between the National Pain Management Committee and facility level pain committees; and a network of VA and non-VA pain-relevant investigators (the Pain Research Working Group) who hold twice monthly teleconferences and yearly face-to-face meetings and who, among their goals, work to promote dissemination of research findings and to influence practice and policy related to pain care. In sum, an established network of resources is already in place to disseminate study findings. Our research group has disseminated study findings in the VA Cyber-seminar forum sponsored by the Center for Information Dissemination and Education Resources (CIDER).

D12. POTENTIAL LIMITATIONS OF PROPOSED STUDY

Generalizability: The study sample will be drawn from a single, VA medical center and three VA community clinics in Indiana. As such, the sample may not be representative of all patients with fibromyalgia. However, the treatments under study could certainly be applied in other VAMCs/CBOCs.

Study design: Our research team thoroughly discussed and debated study design issues. In the end, we agreed to frame POYSE as a fully powered, 2-arm comparative effectiveness trial. However, we strongly considered a 3-arm study to compare yoga vs. structured exercise vs. wait-listed usual care. However, we rejected this alternative for two reasons. The first was pragmatic: it would be difficult to enroll a 50% greater sample size at a single site and this design would add substantially to the trial

costs. Second and more importantly, findings from our recent pain trials have demonstrated the ineffectiveness of usual care for chronic pain management, making a wait list control of less relevance.

Multi-component intervention: The POYSE trial involves a multi-component, yoga intervention that will ***primarily*** test the "bundled" effect (combination of yoga poses, relaxation, and meditation practices) on reduction of overall fibromyalgia severity and associated symptoms. ***Determining the relative effects of the individual yoga components will be difficult, but not impossible. While we considered a study of a less complex intervention, a multi-modal approach is best suited to handle the complexities of fibromyalgia management based on the biopsychosocial model. We also considered either eliminating the meditation component completely or delivering the components sequentially in a stepped-wise fashion rather than concurrently an as an integrated, mind-body, intervention. However, for historical, philosophical, and logistical reasons we decided to deliver the "bundled" yoga intervention as originally proposed.***

To help determine the relative effects and "unbundle" the individual yoga components, we propose two strategies. First, we will conduct post-study, in-depth interviews of a subsample of study participants who receive the yoga intervention. Interview questions will focus on perceptions of which yoga component was most or least helpful, which yoga exercises did participants use most (or least) at home, and patient recommendations to create a "yoga toolbox", i.e., the yoga exercises viewed most effective to reduce fibromyalgia symptoms. Based on our experience with similar qualitative studies, we expect to conduct approximately 25 interviews to improve our understanding of the relative value patients place on the different yoga components (poses, meditation, breathing exercises). We have found qualitative work like this to be highly informative in elucidating trial results. Second, since we expect each component to be an active ingredient, we plan to quantify these components and examine whether there is a dose-response relationship between each component and the primary outcome. We will not control for differential use of components in our main analysis because our main goal is to determine the overall effectiveness of a multi-component yoga intervention.

D13. STRENGTHS AND SYNOPSIS OF STUDY

Despite the study limitations, the POYSE trial has a number of strengths, including: (1) testing the comparative effectiveness of two unique interventions designed to improve the management of fibromyalgia; (2) management approaches that challenge existing treatment paradigms for fibromyalgia care and have the potential to be applied across multiple VA clinical settings; (3) a focus on a significantly understudied fibromyalgia population (men and veterans); (4) a clinical condition that has become frustrating to VA providers; (5) a randomized clinical trial design; (6) ample statistical power to detect meaningful differences in our primary outcome; (7) a large sample size relative to previous trials of yoga and exercise; and (8) an economic evaluation that may provide VA administrators, clinical managers, and policy makers with data to inform budget decisions to invest in these interventions and make them routinely available to veterans suffering from fibromyalgia.

In sum, VA providers are faced with numerous challenges in treating patients with fibromyalgia. The interventions being tested in the POYSE trial have the potential to provide primary care settings with new treatment models that will help to guide VA providers while at the same time providing much needed relief for veterans suffering from fibromyalgia.

APPENDIX A - POYSE Study

with Dr. Matthew Bair

Class #	1	2	3	4	5	6	7	8	9	10	11	12
	Supine, seated and standing practices.		Supine, seated, standing, hands and knees		Supine, seated, standing, hands and knees and prone poses							
Introduction: greetings, goals, benefits, science behind practices.	Intro-duction	Participants will be reminded of these principles throughout course, including interjection of yoga principles/philosophy when relevant.										
Seated or supine	Seated while learning the practices				Once learned, practices are done lying on back							
Breathing / Pranayama	Awareness of breath throughout each session											
• Ujjayi Breathing	Intro-duction	Ujjayi breathing taught first class and practiced throughout all sessions										
• 3 Part Breathing	X	X	X	X	X	X	X	X	X	X	X	X
• establish personal "home base": bandhas and breath	Intro - duction	X	X	"Home base" is reviewed and practiced throughout our course together and as needed for grounding in the moment if/when emotions or sensations escalate out of the window of tolerance: awareness of breath in lower torso with root and belly bandhas								
1. deeper breathing	X	X	X									
2. mula (root) bandha		X	X									
3. uddiyana (belly) bandha			X									
• 2 to 1 Extended Exhale	X	X	X	X	X	X	X	X	X	X	X	X
• Alternate Nostril Breathing				X	X	X	X	X	X	X	X	X
Relaxation w/breath focus	X	X	X	X	X	X	X	X	X	X	X	X
Eye position and movements												
• Drishti	Intro - duction	Drishti (gaze/holding eyes steady) is taught and practiced throughout all sessions.										
• horizontal	X	X	X	X	X	Practiced in closing relaxation						
• circles/clock numbers	X	X	X	X	X							
• diagonal/hourglass	X	X	X	X	X							
• cup eyes in darkness			X	X	X							
Seated series	Seated in chair or on floor with cushion/support as appropriate											
• Neck movements	X	X	X	X	X	X	X	X	X	X	X	X
• Lion Face Pose			X	X	X	X	X	X	X	X	X	X
• Scapular movements, Cactus/Scarecrow Pose	X	X	X	X	X	X	X	X	X	X	X	X
• Seated upper back arch	X	X	X	X	X	X	X	X	X	X	X	X
• Seated side bend	X	X	X	X	X	X	X	X	X	X	X	X
• Seated twist	X	X	X	X	X	X	X	X	X	X	X	X
• Seated "4" Forward Fold	X	X	X	X	X	X	X	X	X	X	X	X

Date				
Blood Pressure				
Aerobic Exercise				
LE ergometer Time (min:sec)/HR				
UE ergometer Time (min:sec)/HR				
Steps Time (min:sec)/HR				
Beginning Strengthening Exercises				
Biceps Curls Sitting/Standing/Ball Repetitions Resistance				
Shoulder Press Sitting/Standing/Ball Repetitions Resistance				
Ball Hug Sitting Repetitions Ball				
Squat Sitting/Standing/Wall Repetitions UE add-in				
Bridge Supine/Ball Repetitions				
Lower Trunk Rotation Supine Repetitions Resistance				
Crunch Supine/Ball Repetitions Rotation add-in UE add-in				
Scapular Retraction Prone/Ball Repetitions UE position				
Hip Abduction Supine/Side/Standing Repetitions Resistance				

Date				
Strengthening Exercise Moderate Progression Options				
Side Lateral Raises Sitting/Standing/Ball Repetitions Resistance				
Upright Rows Standing Repetitions Resistance				
Triceps push-up Sitting Repetitions Up/Anterior LE placement				
Upper Trunk Rotation Sitting/Standing Repetitions Resistance				
Rear Delt Raises Side/Ball Repetitions Resistance				
Lunge Standing Repetitions UE add-in				
Advanced Strengthening Exercise Options				
Push-up Prone/Ball Repetitions				
Plank Prone/Ball Repetitions Time				
Reciprocal Arm/Leg Lift Quad Repetitions Resistance				
Lunge and Turn Kettlebell Repetitions Resistance				
Around the Body Pass Kettlebell Repetitions Resistance				
Date				

Figure 8 Kettlebell Repetitions Resistance				
Swing Kettlebell Repetitions Resistance				
Swing-Snatch Kettlebell Repetitions Resistance				
Stretches				
Upper Trap Repetitions/Time (sec)				
Levator Scapulae Repetitions/Time (sec)				
Lateral Trunk Flexion Repetitions/Time (sec)				
Trunk Rotation Repetitions/Time (sec)				
Hamstring Repetitions/Time (sec)				
Heel Cord Repetitions/Time (sec)				
Quad (LH) Repetitions/Time (sec)				
Pecs Repetitions/Time (sec)				
Lats/Gluts Stretch (prone) Repetitions/Time (sec)				
Staff Name	**Initials (indicate which dates you helped direct exercises for participant)**			