Study title:

Enhancing the Success of Functional Restoration Using Integrative Therapies: Comparative Effectiveness Analysis in Active Duty Service Members with Chronic Pain

Current Approved Protocol

Date of Initial Approval of Original Protocol: 4/28/2015

Date of Approval of Most Recent Protocol Modification: 7/9/20

Today's date: 11/23/20

EIRB Protocol Template (Version 1.2)

1.0 General Information

***Please enter the full title of your study:**

Enhancing the Success of Functional Restoration Using Integrative Therapies: Comparative Effectiveness Analysis in Active Duty Service Members With Chronic Pain

***Please enter the Protocol Number you would like to use to reference the protocol:**

215050
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Is this a multi-site study (i.e. Each site has their own Principal Investigator)?

No

Does this protocol involve the use of animals?

○ Yes ◉ No

2.0 Add Site(s)

2.1 List sites associated with this study:

Primary Dept?	Department Name
◆	**Army** - Madigan Army Medical Center (MAMC)

3.0 Assign project personnel access to the project

3.1 *Please add a Principal Investigator for the study:

FLYNN, DIANE MCFADDEN, MD

Select if applicable

☐ Student ☐ Site Chair
☐ Resident ☐ Fellow

3.2 If applicable, please select the Research Staff personnel:

A) Additional Investigators

SNOW, TYLER JAY
Associate Investigator

B) Research Support Staff

Mcquinn, Honor MARY, DNP
Research Coordinator

3.3 *Please add a Protocol Contact:

FLYNN, DIANE MCFADDEN, MD

The Protocol Contact(s) will receive all important system notifications along with the Principal Investigator. (i.e. The protocol contact(s) are typically either the Protocol Coordinator or the Principal Investigator themselves).

3.4 If applicable, please select the Designated Site Approval(s):

Add the name of the individual authorized to approve and sign off on this protocol from your Site (e.g. the Site Chair).

4.0 Project Information

4.1 Is this a research study?

(•) Yes ( ) No

4.2 What type of research is this?

- [x] Biomedical Research
- [ ] Clinical trial (FDA regulated)
- [ ] Behavioral Research
- [ ] Educational Research
- [ ] Psychosocial Research
- [ ] Oral History
- [ ] Other

4.4 Is this human subjects research (Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by 32 CFR 219.101(a) (including exempt research involving human subjects) and DoDI 3216.02)?

(•) Yes ( ) No

4.5 Do you believe this human subjects research is exempt from IRB review?

( ) Yes (•) No

5.0 Personnel Details

5.1

Will you have a Research Monitor for this study?

- ○ Yes
- ◉ No
- ○ N/A

Research Monitor Role:

If applicable, you may nominate an individual to serve as the Research Monitor:

No Users have been selected.

6.0 Data/Specimens

6.1 Does the study involve the use of existing data or specimens only (no interaction with human subjects)?

○ Yes ◉ No

7.0 Funding and Disclosures

7.1 Source of Funding:

Funding Source	Funding Type	Amount
Congressionally Directed Medical Research Program (CDMRP)	Research Development Testing and Evaluation (RDT&E) funds	999981

Total amount of funding:

999981

7.2 Do you or any other Investigator(s) have a disclosure of a personal interest or financial nature significant with sponsor(s), product(s), instrument(s) and/or company(ies) involved in this study?

○ Yes ◉ No

8.0 Study Locations

8.1 List any Research Team members without EIRB access that are not previously entered in the protocol:

Name: (Last, First, M.I.)	Phone Number:	Email Address:	Associated Institution:

Doorenbos, Ardith Z. Role on Protocol:	206-616-0927	doorenbo@uw.edu	University of Washington
Name: (Last, First, M.I.) Role on Protocol:	Phone Number:	Email Address:	Associated Institution:

8.2 Has another IRB reviewed this study?

○ Yes ◉ No

IRB Name	Review Date	Determination
No records have been added		

8.3 Is this a collaborative or multi-site study? (e.g., are there any other institutions involved?)

◉ Yes ○ No

8.4 Study Facilities and Locations:

Institution	Site Name	Site Role	FWA or DoD Assurance Number	Assurance Expiration Date	Is there an agreement?	IRB Reviewing for Site
	University of WA	Other	00006878	01/29/2025	: CRADA	: RHC - P IRB

Other:

Other Institution Site	Site Role	FWA or DoD Assurance Number	FWA or DoD Expiration Date	Is there an agreement?	IRB Reviewing for Site
No records have been added					

8.5 Are there international sites?

Attach international approval documents, if applicable, when prompted. Note: Ensure local research context has been considered

○ Yes ◉ No

8.6 Is this an OCONUS (Outside Continental United States) study?

○ Yes ◉ No

Select the area of responsibility:

Have you obtained permission from that area of responsibility? (This is a requirement prior to study approval)

○ Yes ○ No

9.0 Study Details

9.1 Abstract/ Summary:

Summarize the proposed study in 500 words or less, to include the purpose, the subject population, the study's design type, and procedures

Pain is an urgent public health concern that significantly impairs the physical, psychological, and social functioning of both those experiencing it and their significant others. The National Center for Health Statistics noted that 40% of people reporting pain indicate moderate to severe degradation in their functioning; this results in tremendous costs to treat or manage the problem. This problem is compounded exponentially by the injuries sustained as a direct result of the recent conflicts in Iraq and Afghanistan. Pain due to musculoskeletal injuries, sustained both on and off the battlefield, is a leading cause of both short- and long-term disability among Soldiers. Pain-related attrition from active-duty is also significant, with only 13% of service members returning to duty in the field when pain is their primary diagnosis. To address these concerns, the Army Surgeon General chartered the Pain Management Task Force (PMTF) in August 2009, to evaluate the state of pain management in the military. The resulting **2010 Pain Management Task Force Report** delineated 109 recommendations to be implemented in phases across the continuum of military medicine and formed the basis for a Comprehensive Pain Management Campaign Plan (CPMCP). Of specific relevance to this proposal, one of the goals of the CPMCP is the **implementation of a Musculoskeletal Action Plan (MAP; PMTF Recommendation 4.2.5)**, that emphasizes the prevention, early identification and proper rehabilitation and reintegration of service members suffering from acute and chronic musculoskeletal injuries related to pain.

Functional restoration (FR) is an intensive, medically-supervised interdisciplinary program, combining quantitatively-directed exercise progression with a multimodal disability management approach, incorporating psychological and case management techniques. This rehabilitation process is a variant of chronic pain management based on the bio-psychosocial model of pain and disability, incorporating a sports medicine approach to rehabilitation. The program is specifically intended for rehabilitation of musculoskeletal injuries, and its effectiveness has been extensively demonstrated in civilian populations as well as preliminary evaluations among injured military personnel. Our ***long-term goal*** is to improve pain management and function for military personnel by facilitating timely and appropriate use of integrative pain management strategies along with a function restoration program.

9.2 Key Words:

Provide up to 5 key words that identify the broad topic(s) of your study

non-pharmacologic pain therapies, integrative, military

9.3 Background and Significance:

Include a literature review that describes in detail the rationale for conducting the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings

The Impact of Pain in the United States

Chronic pain is an urgent public health concern that significantly impairs the physical, psychological, and social functioning of both those experiencing it and their significant others.[1,2] The Institute of Medicine recently estimated that more than 100 million adults in the United States, over one-third of the population, experience some form of chronic pain,[2] with symptoms of pain being the most common

reason people consult a primary care physician.[3] Despite the magnitude of this problem, pain is severely underrepresented in the content of medical education.[4] Consequently, treatment of pain is often fragmented and is highly variable.[5] In addition, the National Center for Health Statistics noted that 40% of people reporting chronic non-cancer pain indicate moderate to severe degradation in their functioning[6] which results in tremendous treatment costs. Specifically, it is estimated that chronic pain costs approximately $635 billion per year in health care and reduced productivity. These costs have increased 5-fold in the past decade and will likely increase with the aging population.[2] However, these increases in health care expenditures have not translated into improvements in clinical outcomes.[7,8] Most importantly, these costs do not reflect the incalculable impact of pain on the lives of patients and their significant others.

In the military health care system, the problems and costs associated with chronic pain are compounded exponentially by the injuries sustained as a direct result of the conflicts in Iraq and Afghanistan. Pain due to injuries sustained both on and off the battlefield is a leading cause of both short- and long-term disability among Soldiers.[9-11] Approximately 48% of military veterans report suffering from pain[12] and 40% who seek care in Veterans Health Administration facilities are diagnosed with a pain condition[13]. De ployment in multiple tours of duty were associated with significantly higher rates of chronic widespread pain.[14] Pain-related attrition from active-duty is also significant, with only 13% of military personnel returning to duty in the field when pain is their primary diagnosis.[15]

The Military Health Care Comprehensive Pain Management Campaign Plan

The Army Surgeon General chartered the Pain Management Task Force (PMTF) in August 2009. This multidisciplinary group of task force members, spanning multiple medical specialties and leadership roles within the Department of Defense (DoD) and the Veterans Health Administration (VHA), was assigned responsibility for evaluating the state of pain management in the military, to identify best pain management practices and to recommend systems of pain care to ensure treatment is implemented in a consistent and uniform manner across the continuum of care. The final report, released as the **2010 Pain Management Task Force Report**, delineated 109 recommendations to be implemented in phases across the continuum of military medicine.[16] Acting on the PMTF report, the Army Medical Department of the Office of the Surgeon General launched a Comprehensive Pain Management Campaign Plan (CPMCP).[17] The CPMCP summarizes the major tasks and objectives of the campaign, notes the importance of implementing tools and infrastructure, and identifies integrative pain management and non-pharmacological therapies as key objectives of the campaign. To realize the objectives of this campaign, several initiatives were identified, including **(1) promoting partnerships between DOD networks and academic institutions to leverage expertise**, and **(2) research on non-pharmacological approaches to pain control using integrative pain management strategies**.

Another significant goal of the CPMCP is the implementation of a **Musculoskeletal Action Plan (MAP; PMTF Recommendation 4.2.5)**, that emphasizes the prevention, early identification and proper rehabilitation and reintegration of military personnel suffering from acute and chronic musculoskeletal injuries related to pain. A major goal of MAP is to evaluate data on outcomes, costs, and return on investment of these rehabilitation-focused treatments. While prevention strategies are critical in reducing the likelihood of occurrence for musculoskeletal injuries, development of adequate early identification and rehabilitative strategies are important to prevent further psychosocial and physical deconditioning, and the subsequent development of chronic pain-related disability. Identifying and implementing an optimal rehabilitative program as part of the military healthcare system's broader pain program is vital to accomplishing the goals of the PMTF. The functional restoration approach to rehabilitation, an intensive interdisciplinary rehabilitation program based on a sports medicine paradigm, may be a significant part in an optimal rehabilitative program. Therefore, the current objectives of military pain medicine underscore the importance of leveraging the expertise of military and civilian clinical programs and research, increasing the use of validated non-pharmacological treatment modalities, and evaluating the effectiveness and value of these initiatives through high-quality research. ***The US Army's CPMCP underscores the importance of two major concepts of this proposal, namely, the implementation of multimodal integrative pain management therapies and a structured interdisciplinary rehabilitation program for military personnel suffering from pain-related disability. More importantly, this proposal aims to systematically investigate the benefits of combined integrative modalities and intensive, interdisciplinary rehabilitation by leveraging the expertise of military and academic pain researchers.***

Table 1. Summary of Pain Management Task Force Recommendations for Enhancing Integrative Pain Management and promoting the Musculoskeletal Action Plan.

Incorporate integrative and alternative therapeutic modalities into a patient-centered plan of care.

1. Adopt a tiered approach for the effective integration of integrative modalities to augment pain management for military and veteran populations.
2. Establish integrative pain medicine capabilities at Department of Defense and Veterans Health Administration Regional Pain Centers of Excellence (RPCoE) and Department of Defense medical treatment facilities (Army, Navy, and Air Force) to champion integrative pain care with a focus on the best clinical practices, education, and research.
3. Establish baseline data on the clinical integrative practices being used, along with provider and patient perspectives, through a comprehensive Department of Defense survey, utilizing existing survey models (if appropriate).
4. Develop an advisory board, with scholarly leaders in various integrative medicine fields, to assist in the development of appropriate programs, ensure proper credentialing of providers, and establish necessary guidelines for outcome measures and uniform quality of care.
5. Establish standardized and appropriate strategic communication plans on integrative health care methods for pain management.
6. Develop and fund pilot programs across the Department of Defense for the delivery of integrative pain management.
7. Request Health Affairs undertake the evaluation of integrative medicine modalities in Tier I (acupuncture, yoga, chiropractic, therapeutic medical massage, biofeedback, mind-body therapies) for inclusion as covered TRICARE benefits.

Musculoskeletal Action Plan: Integrate the prevention, early identification, and treatment of injuries as a component of the comprehensive pain management strategy.

1. Develop an education and STRATCOM program focused on musculoskeletal injury prevention and human performance optimization, early identification, and management, rehabilitation, and reintegration.
2. Integrate the Musculoskeletal Action Plan education program and concepts into the pain education and training program.
3. Create an organizational structure, culture, and climate for awareness and execution of the Musculoskeletal Action Plan by collaborating with DoD and stakeholders within the Army (includes FORSCOM, TRADOC, MEDCOM, USUHS, AMEDD C&S, etc.).
4. Resource prevention and treatment programs that emphasize evidence-based practices. Capture relevant and available data to identify trends, cost, and return on investment. Utilize data to assist in the prioritization of resources.

Army Medicine 2020 Campaign Plan

The Army Medicine 2020 Campaign Plan identifies the priority lines of effort for the Army Medical Department. The Campaign Plan emphasizes the importance of improving rehabilitation, reintegration and recovery through improved pain management. In addition, the Campaign Plan supports intra- and extra-mural research that sustains the DoD pain management mission[18].

Evidence for Increasing the Use of Multimodal Integrative Pain Management in Military Settings

The use of integrative treatment modalities has increased in the United States over the last decade. The National Health Interview Survey reports increasing numbers of Americans using and paying out of pocket for some form of complementary and integrative treatment modality.[19-21] For example, in 2007, over 38% of adults and 12% of children used some form of complementary approach to treatment within the 12 months prior to the survey.[19] Pain complaints were the most common reason for integrative medicine consultations, with back pain being the most common. Other causes of increased interest in integrative pain therapies include the deterioration of the relationship between the patient and health care provider in the allopathic medical system, the growing awareness of serious adverse effects of medications,[22] and the inability of the allopathic medical system to adequately treat chronic disease.[23] ***T here is positive evidence for the effectiveness of integrative approaches to pain management. Several recent systematic reviews and studies, many published in 2013, report the effectiveness of a variety of integrative modalities used to treat pain disorders***.

Acupuncture

A systematic review of acupuncture for nonspecific chronic low back pain, conducted on all published randomized controlled trials (RCTs) on acupuncture through May 2012, yielded 32 studies.[24] Overall, acupuncture had statistically and clinically meaningful improvements in self-reported pain and function when compared to sham procedures. Additional benefits were indicated when acupuncture was used in addition to usual care. However, the authors of that study caution that the results should be interpreted within the context of certain limitations, such as heterogeneity in patient characteristics among the studies, as well as low methodological quality of some of the RCTs reviewed based on methodological quality assessments using the Cochrane risk-of-bias tool. Another recent systematic review examined the effectiveness of acupuncture for lumbar spinal stenosis.[25] This review included six RCTs and nonrandomized controlled clinical trials published in Chinese medical journals. Overall, there was a trend supporting the effectiveness of acupuncture in combination with standard care on pain, function, and quality of life up to 6 months post treatment. Like the previous study, caveats included methodological weaknesses in study design, which warrant more robust research before conclusive evidence can be presented on the effectiveness of acupuncture for treating pain.

Finally, a recently published pilot study conducted at Madigan Army Medical Center (MAMC) investigated the effectiveness of acupuncture, in combination with other complementary adjuvant treatments, for treating generalized anxiety disorder (GAD).[26] Study participants (N = 37) received acupuncture treatments weekly for a 6-week duration, combined with adjuvant treatments such as yogic breathing exercises, self- and/or partner-assisted massage therapy using scented oils, episodic journaling, nutrition counseling, and exercise. Using a pre-to-post comparison, the study reported significant reductions in self-reported anxiety scores on both the Generalized Anxiety Disorder 7-item (GAD-7) and the Depression Anxiety Stress Scale 21-item (DASS-21). Additionally, there was an observed reduction in use of anxiolytic medications. Despite the use of multiple modalities, which may imply treatment burden, voluntary participation and completion of the treatment regimen was modestly high, at a 68% completion rate.

Mind-Body Therapies

Mind-body therapies, which is a broad category composed of modalities such as yoga, Tai Chi, Qigong, meditation, deep breathing, and mindfulness-based therapies, have been used with modest effectiveness for treating psychosocial disorders as well as functional deficits due to pain and disability. A recent systematic review yielded 13 RCTs that investigated mindfulness-based therapies for treating somatization disorders.[27] Compared to control groups, the results indicated moderate effects in favor of mindfulness-based therapy for reducing self-reported pain, symptom severity, depression, and anxiety associated with somatization disorders.

Of specific importance to military medicine, mindfulness-based therapies are also associated with positive treatment effects on patients suffering from post-traumatic stress disorder (PTSD). A review of the literature on the broader application of mind-body techniques (including yoga, Tai Chi, Qigong, meditation, deep breathing, and mindfulness-based stress reduction) indicated significant treatment benefits, including reduced pain, anxiety, anger, and depression; increases in self-esteem, ability to relax, and coping skills; and effective mitigation of PTSD-specific symptoms such as intrusive memories, avoidance, and emotional arousal.[28]

The use of yoga as a primary or adjuvant therapy for chronic pain disorders has also increased in popularity in recent years. Indeed, this modality of mind-body therapy is currently offered to military personnel being treated for pain at MAMC. One systematic review on 10 RCTs that investigated the effectiveness of yoga for low back pain reported positive results.[29] Yoga, in combination with standard care, was associated with strong evidence for both short-term and long-term reductions in pain, as well as short-term improvements in back-specific disability and patients' global perception of improvement. Moderate evidence was also reported for yoga reducing back-specific disability in the long-term. Similar evidence was also observed in a recently published study on the effect of yoga for treating chronic neck pain.[30] However, yoga as a treatment modality for fibromyalgia and rheumatic diseases such as osteoarthritis indicated no beneficial effect.[31]

Another major component of mind-body therapies involves the use of biofeedback as an adjuvant to standard care. Two systematic reviews, which included RCTs as well as nonrandomized controlled trials, indicated relatively small treatment effects for improvement in pain and function following biofeedback modalities.[32,33] However, the aggregated treatment effect in these reviews were likely due to methodological weaknesses in many of these studies that were identified by the systematic reviews. To that end, two recently published studies investigating the feasibility of novel methods of delivering biofeedback support report some promising evidence. These included a biofeedback-based cognitive behavioral therapy modality for patients suffering from temporomandibular disorder,[34] as well as

telehealth delivery of education and biofeedback instruction to women veterans suffering from trauma-induced chronic pain and depression.[35] Both studies indicate preliminary evidence for improvements in pain and function, as well as enhanced coping skills.

Manual Therapies

Within the broad category of manual therapies, chiropractic and therapeutic medical massage are two major modalities that have received considerable attention. To date, systematic reviews on both modalities, when used to treat pain, have indicated some evidence for its benefits. A systematic review investigating the broader modality of manual and manipulative therapies (including chiropractic, in RCT and non-RCT designs) for upper extremity pain and temporomandibular disorder concluded that there is a moderate short-term benefit for reducing pain.[36] Similarly, moderate effects for improving outcomes for pain are also reported for therapeutic medical massage. A systematic review published by the Cochrane Back Review Group reviewed 13 RCTs and concluded that massage may be beneficial for patients suffering from subacute and chronic non-specific low back pain.[37] Two more-recent systematic reviews of massage therapy for low back pain, neck pain, and shoulder pain indicated some benefit in improving pain and function, however, as with chiropractic, the effects were maintained only in the short-term.[38,39] Although these reviews indicate moderate evidence for the beneficial effect of manual therapies, several limitations exist in experimental design within the body of evidence, including heterogeneous patient populations and unstandardized outcome measures across studies that make it challenging to draw strong conclusions about the efficacy of manual therapies.[40] ***The integrative modalities are of significance to the US Army's Comprehensive Pain Management Campaign Plan, and are prioritized for implementation in Army medical treatment facilities. These integrative pain management modalities are currently used to treat military personnel at MAMC.***

The Functional Restoration Approach to Pain and Disability Management

Functional restoration (FR) is an intensive, medically-supervised interdisciplinary program, combining quantitatively-directed exercise progression with a multimodal disability management approach, incorporating psychological and case management techniques.[41] This rehabilitation process is a variant of chronic pain management based on the biopsychosocial model of pain and disability, incorporating a sports medicine approach to rehabilitation. The program is specifically intended for rehabilitation of musculoskeletal injuries in the occupational setting, and its effectiveness has been extensively demonstrated in civilian populations.

The majority of published FR studies to date have been conducted among civilian populations and mainly evaluated the programs' effectiveness at facilitating return to work in low back pain patients with occupational disability.[42-48] Using return to work and/or the number of days of sick leave taken as the main outcome is relevant because the associated costs of disability compensation and productivity losses constitutes a substantial portion of the long-term costs of disability.[49,50] In a systematic review of FR programs for chronic low back pain, FR programs had a positive impact on the return to work rate in the majority of studies (from 65% to 90%).[51] It should be noted, however, that the variation in the return to work rate is likely associated with the social security system of the country where the program was developed. Another possible reason for the different results in the studies might be that study design, patient population, FR program planning, and other external factors were different and therefore not directly comparable. Other outcomes that have been shown to be positively impacted on the long-term (over approximately 5 years) by the FR program include significantly better functioning on activities of daily living, increased physical activity, and reductions in healthcare utilization and days of sick leave.[52]

Notably, several prospective outcome studies have been conducted to explore what clinical characteristics of patients predict success in FR programs. [53-55] This is an important factor, since FR programs are expensive and time intensive. The results of these studies indicated that older age, more days of sick leave, no job availability, and higher pain intensity were significantly correlated to poorer outcomes one year after entry into the study. Other studies have also noted that untreated psychosocial factors and secondary gain motivation predict program non-completion as well as poorer outcomes following FR.[56-59] Notably, the data from these studies suggest that efforts should be made to propose such programs at an earlier stage of disability, and prior attention to psychosocial factors should be conducted as a work-up towards enrolling patients into an FR program.

To date, only one study has been published on the effectiveness of the FR program in a military patient population suffering from pain-related disability.[60] Findings from this study showed positive evidence of FR program outcomes. Participants in the FR program improved significantly compared to the standard treatment group (medication management and injection therapeutics) on self-reported pain, disability, functional status, and fitness for military duty at the post-treatment, 6-month, and 1-year follow-up points. This is the only systematic research study that has been conducted among the military personnel

using standardized functional capacity tests on endurance and lifting strength alongside patient-reported outcomes.[61] ***Functional restoration has extensively improved outcomes in the civilian population and prevented long-term disability while promoting a return to optimal function. To date, no studies in the military healthcare settings have identified prognostic factors for successful completion of FR, as well as maintaining satisfactory long-term outcomes. Additionally, there is insufficient published data on the potential benefits of combining FR with a course of integrative pain management modalities.***

9.4 Objectives/Specific Aims/Research Questions:

Describe the purpose and objective(s) of the study, specific aims, and/or research questions/hypotheses

Aim 1: Evaluate the benefit of a program of multimodal pain management therapies prior to an intensive functional restoration program, relative to standard care.

Hypothesis: Patients who complete an IM program prior to FR will demonstrate significantly greater improvements in pain and physical function going into the FR program, relative to standard care. At post-FR, patients who completed an IM program prior to FR will demonstrate significantly improved outcomes on pain severity and physical function at discharge from the program and at 3-months and 6-months post-FR, relative to standard care.

Aim 2: Identify prognostic factors, including demographic factors, psychologic factors, and readiness factors that predict successful outcomes on pain severity and function, as measured by the Defense and Veterans Pain Rating Scale and PROMIS functional status score, respectively, following intensive interdisciplinary functional restoration.

In addition to IM vs standard care, secondary predictors of outcomes following FR will include: demographic factors (age, military rank, race, household income), psychosocial factors (depression, anxiety, anger); sleep quality and fatigue; medical board status for disability; duration of pain-related disability; prescription opioid dosage; and functional capacity measures of strength and endurance. It is expected that service members with more severe psychological distress and disability at baseline will experience lower rates of positive response following FR.

Aim 3. Evaluate the relationship between legacy paper questionnaires included in the PASTOR-plus packet with PASTOR submeasures.

We will compare legacy paper questionnaires completed by study subjects which include the Tampa Kinesiophobia Questionnaire, Patient Activation Measure, Pain Self-Efficacy Questionnaire, Chronic Pain Acceptance Questionnaire and Roland-Morris Disability Questionnaire, and Pain Catastrophizing Scale with PROMIS measures included in the electronic PASTOR assessment, including pain interference, depression, anxiety, anger, and physical function. This will determine if there are legacy questionnaires with prognostic value which should be added to PASTOR.

Aim 4: Evaluate the relationship between self-reported physical function (from PASTOR) and clinician-supervised tests of physical function, such as exercise treadmill test at all time points.

We will compare self-reported physical function with clinician-supervised tests of physical function to determine if PASTOR respondents over or under-estimate their physical capacity.

Aim 5: Determine whether outcomes differ between the subgroup of participants who completed FR program 4 days per week x 3 weeks vs 2 days per week x 6 weeks

During the course of the study, a protocol modification was approved to allow subjects to participate in the FR program with an extended 2 days per week over 6 week schedule with the same number of treatment hours as the original 4 days per week for 3 weeks. We will evaluate outcomes in both groups to determine if one treatment approach yielded superior outcomes to the other.

Aim 6: Compare outcome measures collected within narrow timelines to those collected within flexible timelines.

We attempted to collect outcome measures at the following timepoints: 1) within one month before starting treatment; 2) within the last day of pre-FR stage through the first day of FR stage; 3) on the last day of FR; 4) 3- and 5) 6- months after the end of FR. However, this precise collection schedule was not always possible. For example, baseline measures were collected more than one month before the start of treatment for study subjects who had conflicts such as military training exercises, personal or family illness or planned leisure travel which postponed the start of study treatment. Collection of follow-up measures was sometimes earlier or later than desired when study subjects with conflicts were unavailable at the time outcomes were requested. We plan to compare outcomes collected within the above timeframes with those collected within timeframes with modest and moderate flexibility as outlined in section 11.3. This analysis will inform the design of future pragmatic clinical trials in determining acceptable timeline parameters for collection of pain outcomes.

Aim 7: Determine if patient activation, pain catastrophizing, self-efficacy or pain acceptance moderates or mediates pain and function outcomes.

We will determine if level of patient activation, catastrophizing, self-efficacy and pain acceptance as measured by legacy questionnaires completed by study subjects have an impact on pain and functional outcomes.

9.5 Study Design:

Describe study design in one to two sentences (e.g., prospective, use of existing records/data /specimens, observational, cross-sectional, interventional, randomized, placebo-controlled, cohort, etc.). Specify the phase – Phase I, II, III, or IV – for FDA-regulated investigational drug research

A comparative effectiveness study, using a prospective randomized cohort design, with patients assigned to either (i) a course of integrative pain management modalities (IM) or (ii) standard care (SC), for three weeks prior to beginning a course of FR.

9.6 Target Population:

Describe the population to whom the study findings will be generalized

Active duty service members with chronic pain

9.7 Benefit to the DoD:

State how this study will impact or be of benefit to the Department of Defense

Improving the quality of pain care for active duty service members is a major priority of the Department of Defense. In 2009, the Army Surgeon General chartered the Pain Management Task Force (PMTF) to evaluate the state of pain management in the military. The resulting 2010 Pain Management Task Force Report delineated 109 recommendations to be implemented in phases across the continuum of military medicine and formed the basis for a Comprehensive Pain Management Campaign Plan (CPMCP). The CPMCP defines several goals and objectives, and these include (1) partnering with DOD and VA networks, civilian, and academic institutions to leverage expertise, and (2) implementing and researching non-pharmacological approaches to pain control using integrative pain management strategies. Of specific relevance to this proposal, one of the goals of the CPMCP is the implementation of a **Musculoskeletal Action Plan** (MAP), which emphasizes the prevention, early identification and proper rehabilitation and reintegration of service members with acute and chronic musculoskeletal injuries related to pain. A major goal of MAP is to evaluate data on outcomes, costs, and return on investment of these rehabilitation-focused treatments. More recently, the **Army Medicine 2020 Campaign Plan** was implemented which emphasizes pain management as a continued priority of the Army Medical Department.

10.0 Study Procedures and Data management

10.1 Study Procedures:

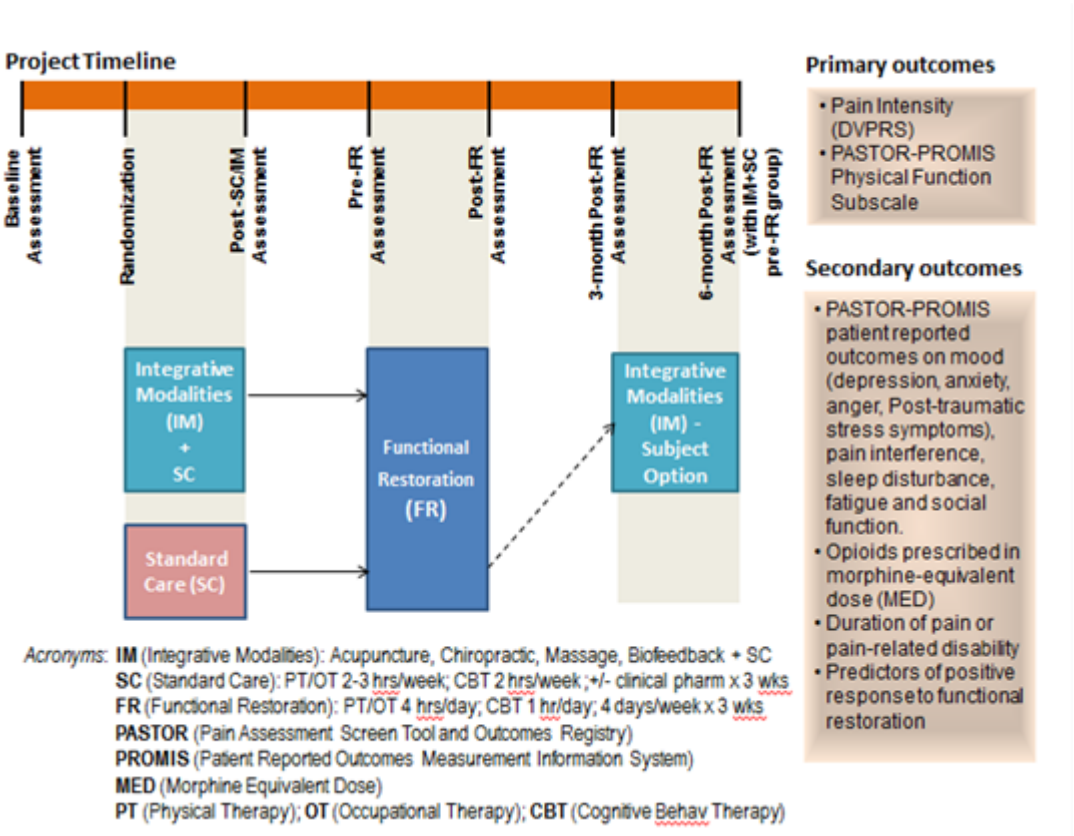
Describe step-by-step how the study will be conducted from beginning to end

Project Setting

The Interdisciplinary Pain Management Clinic (IPMC) at MAMC provides chronic pain care to active duty Soldiers, sailors and airmen in the Puget Sound area. The IPMC has a staff of 32 medical professionals including physicians board certified in anesthesiology, pain medicine, physical medicine, family medicine and palliative care and providers of health psychology, nurse case management, physical therapy, occupational therapy, clinical pharmacology, chiropractic, acupuncture, medical massage therapy and yoga therapy. Structured treatment programs at this facility include the FR and IM programs.

Design

A comparative effectiveness study, using a prospective randomized cohort design, with patients assigned to either (i) a course of integrative pain management modalities (IM) or (ii) standard care (SC), for three weeks prior to beginning a course of FR. Upon completion of the pre-FR treatment arms, all patients will be enrolled into the FR program for the duration of three weeks (up to 96 contact hours; 4 full day session/week). Because it is anticipated that some participants who randomize to the standard FR program may be interested in IM, the standard FR group will be offered the option of IM following completion of the FR program. Outcomes will be collected longitudinally at several time points during the course of the study, including at: (i) baseline, prior to initiation of treatment arms; (ii) completion of pre-FR treatment, before initiation of FR program; (iii) completion of FR program; (iv) 3-months, and 6-mont hs post-FR. Figure 1 illustrates the study design and the multiple points of outcomes assessment throughout the study.



Procedures

Recruitment

All military personnel referred to the Madigan Interdisciplinary Pain Management Clinic have an initial 30-minute orientation group class with a nurse case manager (NCM) who provides an overview of interdisciplinary pain care. At the conclusion of this class, all new patients are provided a laptop computer and instructed to complete the baseline Pain Assessment Screening Tool and Outcomes Registry (PASTOR) questionnaire. Immediately following the IPMC orientation class, all new patients have a 90-minute introduction to the role of cognitive behavioral therapy in pain care. Within the following two weeks, each patient has an initial comprehensive visit with a physician to determine the pain diagnosis and treatment plan.

If the physician determines that the patient is a candidate for the FR program and the patient is willing to commit to this intensive treatment approach, the patient is evaluated by a physical therapist to measure baseline functional status and to determine if he/she has the physical stamina to successfully participate in FR.

The research coordinator or research assistant will perform a brief screen of each potential subject's medical record to determine if he/she has any excluding conditions. If the potential subject has no excluding conditions, the research coordinator or research assistant will meet with him/her to explain the study and to request their consent for study participation. The commanding officer for each subject will be contacted and asked to approve the subject's absence from work as needed for the 6-9 week program.

Randomization

Then, each patient will be randomized to one of two treatment groups: the standard FR program or the FR + integrative modalities (IM) program. Because it is assumed that some participants who randomize to the standard FR program may be interested in IM, the standard FR group will be offered the option of IM following completion of the FR program. The components of the intervention and control treatments are shown in Table 2.

Standard care is comprised of twice weekly health psychology group therapy, twice weekly physical therapy and once-twice weekly occupational therapy during the three weeks prior to FR. Participants on chronic opioid therapy will also be seen by a clinical pharmacist for evaluation for opioid taper. The IM program is comprised of twice weekly acupuncture and chiropractic and once weekly yoga and myofascial release instruction by massage therapist. If indicated, biofeedback and individual massage may also be used. The FR program includes four full days of therapy per week for three weeks. Each FR treatment day will include approximately four-hours of physical activity and one hour each per day of health psychology group therapy and an educational session. Examples of the daily schedules for SC, IM and FR is shown in Figure 2. In an effort to meet enrollment targets, patients who are otherwise eligible for FR program participation but cannot commit to 4 full days of therapy for a three-week period will be given the option of 2 full days of therapy over a six-week period for the same number of contact hours.

Table 2. Intervention and Standard Care

	Approximate Contact hours	Intervention Group	Control Group
Standard Pre-FR Care (SC)			
CBT 90-minute orientation	90-minutes	X	X
Health psychology / CBT group therapy	2 hrs/wk x 3 weeks	X	X
Physical therapy/occupational therapy warm-up	2-3 hrs/wk x 3 weeks	X	X
Clinical pharmacist evaluation (if taking opioids)	1-2 hours during 3 weeks	X	X
IM prior to FR:	**3 weeks comprised of:**		
Chiropractic	15-minutes, twice per week	X	
Acupuncture		X	
Yoga	1-hr, twice per week	X	
Biofeedback (if indicated)	1-hr per week	X	
	45-min per week	X	

Foam roller class Medical massage (if indicated)	1-hr per week 1-hr every other week	X	
FR program: Physical training Health psychology/CBT group therapy Didactic education	**3 weeks comprised of:** 4-hrs per day, 4 days per week 1-hr per day, 4 days per week 1-hr per day, 4 days per week -or- **6 weeks comprised of:** 4-hrs per day, 2 days per week 1-hr per day, 4 days per week 1-hr per day, 4 days per week	X X X X X X	X X X X X X
IM after FR: Chiropractic Acupuncture Yoga Biofeedback (if indicated) Foam roller class Medical massage (if indicated)	**3 weeks comprised of:** 15-minutes, twice per week 1-hr, twice per week 1-hr per week 45-min per week 1-hr per week 1-hr every other week		X (patient option) X (patient option) X (patient option) X (patient option) X (patient option) X (patient option) X (patient option)

Patient-Reported Outcomes

Patient demographic data and patient-reported outcomes will be collected using the DOD's Pain Assessment Screening Tool and Outcomes Registry (PASTOR).[62] This Web-based patient-reported outcomes tool, currently used at Madigan IPMC,[63] was designed to reduce the burden of patient questionnaires during clinical contact through modern information technology and to make use of **well-established and validated pain-related assessments** already available. It uses the computerized adaptive learning system of the Patient Reported Outcome Measurement Information System (PROMIS), which contains a large, validated databank of all surveys from the literature and was developed by the National Institutes of Health (NIH). Notably, PASTOR is one of the major recommendations from the 2010 Army Pain Management Task Force Report. PASTOR will serve two major purposes: first, it will collect longitudinal outcomes data on patients treated in military hospitals in an outcomes registry; and second, it will provide a summary outcomes report on each patient for the IM and FR clinical team for review at during each assessment period. The PASTOR outcomes report (which includes the specific outcomes and treatment data collected) is presented in Section 6: Surveys, Questionnaires, and Other Data Collection Instruments – PASTOR. It is currently beginning a beta-test phase in select Army and Navy medical treatment facilities (including MAMC), and will be implemented during 2015-16 as standard of care for pain assessment at Army hospitals nationwide.

All patients will complete scheduled assessments according to the following timeline of the study:

1. At baseline, prior to randomization to SC or IM

2. At completion of SC or IM, prior to initiation of FR program

3. At completion of FR program

4. At 3-months post-FR program

5. At 6-months post-FR program

Table 3. Patient-Reported Outcome Measures in PASTOR
Primary Outcomes
Defense and Veterans Pain Rating Scale (DVPRS)[64] • Pain Intensity 10-pt Numeric Rating Scale (NRS) Physical Function Subscale of PROMIS Global Health[65]
Secondary Outcomes
PROMIS Pain Interference[66]
PROMIS Depression[67]
PROMIS Anxiety[67]
PROMIS Emotional Distress - Anger[67]
PROMIS Sleep Disturbance[68]
PROMIS Fatigue[69]
Patient-defined activity goal[70]
Patient Activation Measure (PAM)[71]
Drug Use Questionnaire (DAST-10)[72]
Pain Catastrophizing Scale (PCS)[73]
Tampa Scale for Kinesiophobia (TSK11)[74]
Pain Self Efficacy Questionnaire (PSEQ)[75]
Chronic Pain Acceptance Questionnaire (CPAQ8)[76]
Canadian Occupational Performance Measure (COPM)[81]
Roland-Morris Disability Questionnaire[80]
Opioid utilization screener* • Current opioid regimen • Duration of pain and of opioid treatment • Morphine equivalent dose • Pain relief from opioids**
**Data on utilization and dosage are electronically extracted by PASTOR from the CHCS Electronic Medical Database.* ***Patient self-reports pain relief if applicable.*

Based on six months of experience with use of PASTOR at the Madigan Interdisciplinary Pain Management Center, the time required to complete this study's PASTOR measures is expected to be

approximately 20 minutes at baseline and 15 minutes at each follow-up time point. Because the PASTOR platform is a secure, web-based system, participants will have the option of completing PASTOR from the convenience of their homes. The psychometrics of PASTOR are discussed in section 7.3.4.

Upon completion of a PASTOR assessment, a three-page report is generated (see Section 6: Surveys, Questionnaires, and Other Data Collection Instruments – PASTOR) that summarizes all domains measured and displays them longitudinally once there are two or more assessments completed. Raw data will be stored in the PASTOR outcomes registry and made available to the research study after patient identifiers have been removed. It is planned that PASTOR will eventually include other validated measures relevant to pain, including the Patient Activation Measure, Pain Catastrophizing Scale, Tampa Scale for Kinesiophobia, Pain Self-efficacy Questionnaire and Chronic Pain Acceptance Questionnaire. Until these measures are added to electronic PASTOR assessment tool, these additional questionnaires will be administered in paper form at the same intervals that PASTOR is administered.

In February 2016, the Army Functional Restoration Workgroup determined that the Rolland-Morris Disability Score and the Canadian Occupational Performance Measure should be among the standardized outcome measures used by all Army FR programs, so these outcome measures are also included.

Upon the completion of the functional restoration program participants will complete the global improvement scale in order to support psychometric analysis to determine the minimal importance difference for primary outcome variable – pain impact score. This will require the addition of a 1-2 questions to the current paper-based questionnaire administered at the post-FRP time interval.

Functional Tests on Endurance and Isokinetic Lifting Strength and Flexibility

Functional capacity tests on endurance and lifting strength are standard outcomes used in FR programs, to complement patient-reported outcomes. These functional measures, similar to that used to screen patients for the inclusion criteria, include[61]:

- **Naughton Treadmill Test:** Measures the pace and duration of time on a treadmill. It is expected that with improved functional capacity after FR, patients will be able to endure a faster treadmill pace for a longer duration of time.
- **Floor-Knuckle Lift Test:** Lifting weights from floor to knuckle height. It is expected that with improved functional capacity after FR, patients will be able to lift heavier weights.
- **Floor-Shoulder Lift Test:** Lifting weights from floor to shoulder height. It is expected that with improved functional capacity after FR, patients will be able to lift heavier weights.
- **40-ft Carry Test:** Carrying a weight and walking at least 40-feet in distance. It is expected that with improved functional capacity after FR, patients will be able to carry heavier weights over the 40-feet distance.
- **7-to-1 Pyramid Test**: The 7-1 pyramid is a functional physical assessment that consists of push-ups, back extensions, rowers, squats, dips, and burpees. The patient will begin with 7 repetitions of the listed exercises, then 6 repetitions of each exercise, and so on down to 1 repetition of each exercise. The patient completes as many as possible in 10 minutes. If the patient is able to get to 1 repetition of each exercise then the pyramid starts over with 8 repetitions of each exercise, then 7, and so on down to 1. There are 3 specific modifications for each of the 6 different exercises. If a patient is unable to complete the exercise in the specified way then the patient will be shown modification #1 and so on through modification #3 if necessary. The patient is scored on total repetitions completed.

10.2 Data Collection:

Describe all the data variables, information to be collected, the source of the data, how the data will be operationally measured, and approvals needed for use of information from DoD databases

Table 8. Data Collection Variables

Variable	Data Source	Time points
Demographic data	DHA SDD, PASTOR	Baseline
Pain intensity	DVPRS (PASTOR)	

Physical function	Subscale of PROMIS Global Health (PASTOR)	Baseline, before and after SC; before and after FR; 3- and 6-months post-FR
Pain interference	PASTOR	
Depression	PASTOR	
Anxiety	PASTOR	
Emotional distress-anger	PASTOR	
Sleep disturbance	PASTOR	
Fatigue	PASTOR	
Patient-defined activity goal	PASTOR	
PAM	PASTOR	
DAST-10	PASTOR	
PCS	PASTOR	
TSK	PASTOR	
PSEQ	PASTOR	
CPAQ8	PASTOR	
Current pain medications	PASTOR, CHCS	
Morphine-equivalent dosage per day	DHA SDD	
Current pain relief from medications	PASTOR	
Functional measures (floor-knuckle and floor-shoulder lift tests, 40ft carry test, McNaughton treadmill test, 7-to-1 Pyramid measures)	As measured by a physical therapist	

Pain Intensity and PROMIS Measures

The individual validated scales and clinical screening tools in PASTOR are summarized in Table 3. **Pain intensity** will be rated on a 0 – 10 scale (0 = no pain, 10 = worst possible pain). All PROMIS measures are administered using computerized adaptive testing, thus ensuring a low response burden to the patient. The recall period is 7 days. The PROMIS **pain interference** item bank specifically focuses not on the more commonly measured pain intensity, but on pain interference, defined as interference of pain in daily activities involving physical, psychological, and social functioning. The PROMIS **depressive symptoms** consist of items that address sadness, loss of interest, worthlessness, low self-esteem, loneliness, and interpersonal alienation. The PROMIS **anxiety** consists of an item bank that addresses fearfulness, worry, and nervousness. The PROMIS **emotional distress – anger** item bank assesses angry mood, negative social cognitions, verbal aggression, and efforts to control anger. The PROMIS **global health** item pool assesses health in general. The global health items include global ratings of the five primary PROMIS domains, physical function, fatigue, pain, emotional distress, social health, as well as perceptions of general health that cut across domains. The PROMIS **sleep disturbance** item bank assess perceptions of sleep quality, sleep depth, and restoration associated with sleep; perceived difficulties and concerns with getting to sleep or staying asleep; and perceptions of the adequacy of and

satisfaction with sleep. The PROMIS **fatigue** consists of items that address fatigue from mild subjective feelings of tiredness to overwhelming and sustained sense of exhaustion. PASTOR also includes 11 items related to prior and current treatment modalities; 5 items asking about health care utilization and a 3 item opioid utilization screener.

Supplemental Assessments

PASTOR also includes a battery of supplemental assessments that are relevant for screening and monitoring patient outcomes on several other domains of importance to patients enrolled in a functional restoration program.

These measures are also summarized in Table 3 above. The Patient Activation Measure (PAM) [71] is a 22-item survey on four stages of activation: (1) believing the patient role is important, (2) having the confidence and knowledge necessary to take action, (3) actually taking action to maintain and improve one's health, and (4) staying the course even under stress. The PAM demonstrates excellent reliability (Cronbach's alpha = 0.91), and strong evidence for construct validity in differentiating health status by activation levels ($r = 0.38$, $p < 0.01$). The Drug Abuse Screen Test (DAST-10)[72] is a short-form clinical screener for potential drug abuse and was initially developed based on the criteria for the Diagnostic and Statistical Manual for Mental Disorders (DSM III-R). The measure has excellent discriminant validity between patients with lifetime drug abuse disorders and those without the diagnosis (correctly classifies > 93% based on Receiver Operating Characteristic analysis). The Pain Catastrophizing Scale (PCS) [73] is a 13-item three-dimension survey of catastrophizing that include items measuring a patient's tendency for (1) rumination, (2), magnification, and (3) helplessness. The PCS demonstrates excellent discriminant validity in context of both experimental pain and clinical pain, with higher PCS scores strongly correlated with negative pain-related thoughts, emotional distress, and greater perceived pain. The Tampa Scale for Kinesiophobia (TSK-11)[74] is an 11-item survey assessing pain-related fear of physical activity in patients with back pain. The TSK-11 has good internal consistency (Cronbach's alpha=0.79), test-retest reliability (ICC=0.81, SEM=2.54), and responsiveness (SRM=-1.11). The Pain Self-Efficacy Questionnaire (PSEQ)[75] is a 10-item survey assessing patients' self-efficacy beliefs with respect to their pain, and has excellent internal consistency (Cronbach's alpha = 0.92), test-retest reliability ($r = 0.73$), and construct validity against other domains of health such as mental health, pain assessments, and coping behaviors. Lastly, the Chronic Pain Acceptance Questionnaire (CPAQ-8)[76] is an 8-item survey of (1) the degree to which patients engage in life activities regardless of pain (activity engagement), and (2) willingness to experience pain, or the inverse of engaging in behaviors to limit pain (pain willingness). The CPAQ-8 had good internal consistency (Cronbach's alpha = 0.77 – 0.89) and demonstrated good construct validity against other domains of health such as depression, anxiety, pain interference and pain severity. The reliabilities of the supplemental assessments will be applied for correction for attenuation in future analyses whenever applicable.

Authors' approval to include the PCS, TSK11, PSEQ and CPAQ-8 assessment tools in PASTOR has been obtained and copies have been uploaded to IRBNet. Author approval to use the PAM is pending. If not received, this tool will be omitted from PASTOR. A licensure agreement has been established for use of the DAST10 tool.

Standardized Army FR Outcomes. In February 2016, the Army Functional Restoration Workgroup met to decide on a standard set of outcome measures to be implemented in all Army FR programs. In addition to the measures included in the original protocol, the workgroup determined that the Canadian Occupational Performance Measure, Rolland-Morris Disability Score and the 7-to-1 Pyramid Test would also be measured at each Army FR program.

Psychometric analysis of the minimal important difference for the Pain Impact Score. The NIH Taskforce on Standards for research on low back pain recommend measuring the pain impact score, a composite score which includes consideration of pain intensity, physical function and pain interference[1]. In 2016, Deyo, et al[2] reported good psychometric performance of the PROMIS Pain Impact Score and suggested that the Pain Impact Score was a meaningful outcome measure for any musculoskeletal pain condition. Because PASTOR already collects the component measures of the pain impact score, the pain Impact Score was previously selected as the primary outcome measure for this study.

In order to compute the number needed to treat to achieve benefit, the minimum important difference (MID) must be known. The MID for the Pain Impact Score has not yet been empirically determined; however, it has been proposed that an improvement or worsening of 3 or greater is a reasonable estimate of the MID.[2]

The MID for other pain outcomes, such as pain intensity was empirically determined by asking the questions we propose to add to the questionnaire completed by study subjects at the completion of the functional restoration program.[3,4] We propose to collect preliminary data during the remainder of this study to determine if a specific change in pain impact score correlates with different levels of subjective

improvement or worsening. This analysis will contribute to understanding of the minimum importance difference in the Pain Impact Score and will contribute to future research that uses the Pain Impact Score as an outcome measure.

Management of Collected Data

Data metrics from all surveys will be stored within data collection sheets which include: Bio-Forward Flex Tracker, COPM Database Tracker, Enrollment Log Tracker, Functional Measures Database Tracker, Pastor Plus Database Tracker, and a Pyramid Measures Tracker. Clinical research staff will maintain these data collection sheets with assistance from the IPMC medical providers who collect the data during study visits.

The PI will manage, maintain, and secure all study documents and materials. The PI as the primary control point, combined with a small supporting research team, will help protect against disclosure.

10.3 At any point in the study, will you request, use, or access PII from the Military Health System (MHS)?

(•) Yes ( ) No

10.4 Have you consulted with an MHS data expert to determine the data elements to be extracted or the information system(s) to access?

Consulting with a data expert often saves time later in the compliance process because the data expert can advise on the data available in the numerous MHS information systems, the quality of that data and the methods for encrypting and collapsing data. To schedule a consult with an MHS data expert, send an email to: (**dha.ncr.pcl.mbx.privacyboard@mail.mil**)

(•) Yes, then complete the questions below according to the data consult
( ) No, then complete the questions below according to the best of your knowledge (NOTE: It is highly recommended that you work with an MHS data expert)

10.5 Indicate whether you plan to receive a data extract from the MHS or plan to access an information system directly to create a data set:

A data extract is when the MHS or a contractor provides the data set directly to the researcher. When receiving a data set through data extract, the researcher may indicate whether the data elements should be provided as is, encrypted or collapsed. In contrast to a data extract, access to an information system means that the researcher may directly access an MHS information system and create a data set for the research study

[x] Data Extract
[ ] Access

10.6 Do you intend to use only de-identified data from the MHS in your research study?

There are different two methods for de-identifying data pursuant to HIPAA:
1) Safe Harbor Method: Removing all of the identifiers listed in Table 1 below, provided that the researcher does not have actual knowledge that the remaining data can be used alone or in combination with other information to identify the individual who is the subject of the information
2) Statistical Method: An expert, with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable, determines that the data is not individually identifiable

( ) Yes (•) No

10.7 If your research study requires access to an MHS information system, please indicate the system to obtain data:

If you do not know which system(s) contain the data elements you need, refer to the Guide for DoD Researchers on Using MHS Data or seek guidance from an MHS data expert:

PHI Systems:

MHS Information System	Requesting Data
AHLTA	Yes
M2	Yes
PDTS	Yes

PII-Only Systems:

MHS Information System	Requesting Data

De-Identified Data & Other Systems:

Information System	Requesting Data
Expense Assignment System	
DHA Opioid Registry	Yes
Army PASBA	Yes

10.8 Do you intend to merge or otherwise associate the requested data with data from any sources outside of the MHS, including other DoD systems that are not part of the MHS?

- ○ Yes, will merge data
- ◉ No, will not merge data

10.9 Indicate the categories of data that you will request from MHS systems or MHS health care providers about research participants or relatives, employers, or household members of the research participants.

Data Element(s)	MHS	Non-MHS Systems
1. Names	☐	☐
2. Postal address with only town, city, state and zip code	☐	☐
3. Postal address with all geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of Census: 1) the geographic unit formed by combining all zip codes with the same three initial digits	☐	☐

contains more than 20,000 people; and 2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000		
4. Dates including all elements (except year) directly related to an individual, including birth date, admission date, discharge date, and date of death	☑	☐
5. Ages over 89 and all elements of dates (including year) indicative of such age, unless you will only request a single category of "age 90 or older"	☐	☐
6. Telephone numbers	☐	☐
7. Fax numbers	☐	☐
8. Electronic mail addresses	☐	☐
9. Social Security numbers (SSNs)	☐	☐
10. Medical record numbers	☐	☐
11. Health plan beneficiary numbers	☐	☐
12. Account numbers	☐	☐
13. Certificate/license numbers	☐	☐
14. Vehicle identifiers and serial numbers, including license plate numbers	☐	☐
15. Device identifiers and serial numbers	☐	☐
16. Web Universal Resource Locators (URLs)	☐	☐
17. Internet Protocol (IP) address numbers	☐	☐
18. Biometric identifiers, including finger and voice prints	☐	☐
	☐	☐

19. Full-face photographic images and any comparable images		
20. Any other unique identifying number, characteristic, or code (DEERs ID, EDIPN, Rank)	☑	☐

If you are obtaining SSNs, provide a justification as to why and explain why a substitute cannot be used

10.10 Is it possible that the data will become identifiable because of triangulation, a small cell size, or any unique data element(s)?

Triangulation means using different data elements that are not themselves identifiable but that when combined can be used to identify an individual. For example, triangulation would be using rank and race together to determine the identity of an individual with a particular health condition
Small cell size means that there are only a small number of eligible individuals that satisfy the category description. Guidance for acceptable cell size is available from the Centers for Medicare and Medicaid Services. For example, the rank category of four star generals with a particular diagnosis may be less than 30 so the rank category may need to be expanded to include lower ranks
A unique data element includes any unique features that are not explicitly enumerated in the categories of data in rows 1 – 19 of Table 1 above, but that could be used to identify an individual. Examples of unique data elements include: 1) a unique number, such as a medical record number or EDIPN; 2) a unique code, such as a diagnosis code or a bar code on an electronic health record; and 3) any unique characteristic, such as the rank of general or admiral, or a race or gender combined with another unique characteristic

- ○ Yes, there is a reasonable possibility the data will become identifiable
- ◉ No, there is no reasonable possibility the data will become identifiable

10.11 HIPAA Privacy Rule and Use of Protected Health Information in Research:

- ○ N/A – will not use or disclose protected health information (PHI)
- ○ HIPAA Authorization will be obtained
- ○ Use of a limited data set where a data use agreement will be obtained
- ◉ Waiver/alteration of HIPAA Authorization is being requested

10.12 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for this Study:

Include in this section the plan for acquiring data (both electronic and hard copy), access during the study, data/specimen storage and length of time stored, shipment/transmission, and the plan for storage and final disposition at the conclusion of the study. Describe any data agreements in place for accessing data within and/or outside of your institution (e.g., Data Sharing Agreement, Data Use Agreement, Business Agreements, etc.)

The following is an explanation of how study data will be managed.

1. Master Key. Will include information on the name, date of birth and Social Security number for each study subject and documentation that each is a suitable study subject based on inclusion /exclusion criteria. These data will be maintain in an excel spreadsheet on a secure, password-protected server.
2. Subject data sheets. Will include each study subjects study ID number, their age, military rank, military occupational specialty (MOS), military unit, date consent obtained, result of randomization, starting and ending dates of participation in standard care, integrative modalities care and functional restoration and functional outcome measures (floor-knuckle lift test; knuckle-shoulder lift test, 40-foot carry test and Naughton treadmill test). Final data analysis of this de-identified data will be done at the University of Washington.

3. Informed consent forms. Will be stored in a locked file cabinet at Madigan Army Medical Center (MAMC) in the office of the study administrative staff.

4. PASTOR data. Study subjects will complete PASTOR electronic questionnaires periodically during the study period. PASTOR is managed by the Army Analytics Group (AAG). PASTOR data for study subjects will be transferred using AMRDEC to the Defense Health Agency Solution Delivery Division (DHA/SDD) to be merged with data compiled by DHA/SDD (and explained in #10 below). Patients will have access to their responses and the trends of those responses over time. All Interdisciplinary Pain Management Clinic (IPMC) providers and primary care providers involved in the care of these patients will have access to PASTOR results.

5. Physical therapy functional measures. Each patient will have pre- and post-intervention assessments by a physical therapist. These data will be maintained on a secure, password-protected server. Physical Therapy (PT) measures are the standard of care for patients enrolled in the Functional Restoration (FR) Program and are available to the entire FR provider team.

6. Surface –EMG measures. Each patient will have pre- and post-intervention surface electromyography assessments to measure muscle tension. These measurements will be maintained on a secure, password-protected server.

7. Opioid Dosage. Opioid dosage and Risk Index of Serious Overdose or Respiration Depression (RIOSORD) score will be derived from the DHA Opioid Registry and recorded at baseline, at the conclusion of stage 2 treatment and 3 and 6 months post treatment. These data will be compiled by the DHA/SDD through an approved data sharing agreement explained in #10 below.

8. Military Medical Readiness. Military medical readiness will be compiled from the Army Medical Protections System (MEDPROS) by the Defense Health Agency Clinical Support Program Solution Delivery Division through an approved data sharing agreement using the same process to be used for opioid dosage and explained in #10.

9. Treatment hours. Number of contact hours in the Interdisciplinary Pain Management Center for medical providers, physical therapy, occupational therapy, health psychology, chiropractic, acupuncture, yoga and massage, nurse case management, education as well as interventional procedures will be tracked from the baseline period through up to six months after completion of therapy. These data will be compiled by the Defense Health Agency Clinical Support Program Solution Delivery Division through an approved data sharing agreement using the process to be used for opioid dosage and explained in #10.

10. Process for data sharing. Data sharing agreements will be established between 1) the PI, DHA /SDD and the University of Washington, as well as 2) the PI, PASBA, DHA/SDD and the University of Washington and will reflect the following process:

11. The MAMC PI will securely transfer to DHA/SDD a list of consented study subjects, including: name and EDIPN, randomization group, date of randomization and dates of study treatment start and completion.

12. The MAMC PI will also securely transfer to DHA/SDD outcome measures collected at MAMC including PASTOR and PASTOR Plus measures and Canadian Occupational Performance Measure.

13. PASBA will provide baseline and end-of-study military readiness status to DHA/SDD.

14. DHA/SDD will extract all requested data from applicable databases and merge with data provided by the PI and PASBA.

15. DHA/SDD will de-identify the merged data per HIPAA guidelines, assign pseudo-identifiers and securely transfer to the University of Washington researchers for analysis.

16. At the end of the study, the PI and the research team at the University of Washington will delete any data related to the study.

17. PASTOR, physical therapy, and surface EMG data will be accessible to IPMC's providers involved in the care of each patient. PT measures are accessible to the entire FR clinical team. Only research personnel and representatives of USAMRMC will have access subject data sheets and consent forms.

18. Data Security Procedures for Transfer, Implementation, and Storage of Data: All computers used to collect and send data during implementation of the study or to receive or store data at the central location will be password-protected. A password will be required to open Windows and a different password will be required to open the customized protocol software. Electronic information will be stored on the secure dedicated server with appropriate firewalls. Servers are scanned for viruses, and systems are in-place to detect attempts at unauthorized entry.
19. Data Transfer Procedures: Transfer of protocol data will occur by a secure data transfer site used by DHA/SDD. These data are stored on a dedicated server protected from viruses and unauthorized entry.

10.13 Managing Data (Data Management and/or Sharing Plan) and/or Human Biological Specimens for Future Research:

If the study involves collecting, storing, or banking human specimens, data, or documents (either by the Investigator or through an established repository) for FUTURE research, address. How the specimens /data will be used, where and how data/specimens will be stored (including shipping procedures, storage plan, etc.), whether and how consent will be obtained, procedures that will fulfill subjects' request as stated in the consent, whether subjects may withdraw their data/specimens from storage, whether and how subjects may be recontacted for future research and given the option to decline, whether there will be genetic testing on the specimens, who will have access to the data/specimens, and the linkage, the length of time that data/specimens will be stored and conditions under which data/specimens will be destroyed

Not applicable

11.0 Statistical/Data Analysis Plan

11.1 Statistical Considerations:

List the statistical methods to be used to address the primary and secondary objectives, specific aims, and/or research hypotheses. Explain how missing data and outliers will be handled in the analysis. The analysis plan should be consistent with the study objectives. Include any sub-group analyses (e.g., gender or age group). Specify statistical methods and variables for each analysis. Describe how confounding variables will be controlled in the data analysis

The statistical methods that will be used for each study aim are explained in section 11.3.

Approach to Missing Data.

The amount of missing data will be first quantified where possible, and determined by the amount of missing data that occurs, three indirect tests of the mechanism of missingness will be explored: (1) baseline demographic characteristics of those who ever and never missed data by group allocation will be compared (an indirect test to rule out missing completely at random [MCAR]); (2) the difference between mean utility scores of participants with missing and non-missing data will also be compared (an additional indirect test to rule out MCAR) and (3) controlling for the probability of providing missing data, the mean scores of those that never and ever missed in intervention and control groups will be compared (an indirect test of missing not at random [MNAR]). While analysis using mixed models allows all observed data to be included in the analysis under the assumption that the data are MCAR, if substantial missing data occurs, multiple imputation or mean conditional imputation will be used with subsequent sensitivity analyses to explore the impact of imputation on results. To address the issue of artificially reduced estimates of stochastic uncertainty produced by imputation, bootstrapping procedures will be used on the entire imputation and estimation process.

11.2 Sample Size Estimation:

Estimated required sample size: 152
Estimated participant drop out + withdrawal: 28%
Total enrollment requirement: 210
Total MAMC enrollment: 210

11.3 Data Analysis Plan:

Primary (i.e., primary outcome variables) and secondary endpoints. The primary outcome endpoints are pain intensity and functional status as measured by the PASTOR questionnaire. In addition, secondary predictors of outcomes measures will be evaluated, including demographic factors (age, military rank, household income, race), measures of pain interference, depression, anxiety, anger, sleep quality, fatigue, medical board status for disability, duration of pain-related disability, prescription opioid dosage and functional capacity tests for endurance and strength.

Data analysis.

Aim 1: Evaluate the benefit of a program of multimodal integrative pain management therapies prior to an intensive functional restoration program, relative to standard care.

Hypothesis: Patients who complete an IM program prior to an FR program will demonstrate significantly greater improvements in pain and physical function going into the FR program, relative to standard care. At post-FR, patients who completed an IM program prior to FR will demonstrate significantly improved outcomes on pain severity and physical function at discharge from the program and at 3-months post-FR, relative to standard care.

Analytical Technique: We will use a hierarchical linear model (HLM) for a cluster-randomized trial with time nested within patients.[77] HLM affords an integrated approach to studying the structure and predictors of individual change, and provides the appropriate standard errors and correct statistical inferences for clustered data. HLM models allow the use of data from patients who are missing one or more observations, where the assumption holds that data are missing at random. Some patients will not follow the intervention protocol, either deliberately by not doing the intervention or due to extenuating circumstances that prevent their participation with the intervention protocol. We will use an intent-to-treat analysis.

We will initially complete analyses without the inclusion of pre-randomization covariate information. In all analyses, the data will be examined for appropriateness of the statistical assumptions underlying fitted models (e.g., distribution of regression residuals, identification of multivariate outliers representing influential data points, tests for departures from linearity). The primary analysis will examine differences between the control and intervention groups' outcome scores at the 3 month assessment point. To control for inflation of Type I error rates due to co-primary outcomes, alpha will be set to 0.025 for each test of the outcome variables.

If recruitment targets are exceeded to a sufficient magnitude, secondary analyses of change in pain severity and physical function using responder analysis will also be performed. When consensus on minimally important difference (MID) exists, that MID will be used to define response. For PROMIS measures that do not have consensus MID measures, an improvement of one-half of one standard deviation on the PROMIS scale will be considered the minimally important difference for a positive response. Responder analyses require higher sample sizes to detect statistically significant differences but are the preferred method of assessing treatment effect, and permit meaningful comparisons between randomized clinical trials. [78]

Aim 2: Identify prognostic factors that predict successful outcomes on pain severity and function following intensive interdisciplinary functional restoration.

In addition to IM vs standard care, secondary predictors of outcomes following FR will include baseline measures of: demographic variables (age, military rank, race, military occupation), pain characteristics (location, duration, character), psychosocial factors (depression, anxiety, anger); sleep quality and fatigue; medical board status for disability; duration of pain-related disability; prescription opioid dosage; and functional capacity tests for endurance and strength.

Analytical Technique: The co-primary outcomes for pain severity and physical function will be analyzed using a Sequential Multiple Regression model.[79] The model will adjust for baseline measures of the co-primary outcomes and pre-FR treatment groups, before assessing the relative importance of secondary outcomes measures (baseline measures of pain interference, depression, anxiety, anger, sleep quality, fatigue, medical board status for disability, duration of pain-related disability, prescription opioid dosage, and functional capacity tests for endurance and strength). Relative importance of predictors among these secondary outcomes will be reported by their respective regression beta weight coefficients. To control for inflation of Type I error rates due to co-primary outcomes, alpha will be set to 0.025 for each test of the outcome variables in their respective regression models.

Aim 3: Evaluate the relationship between legacy paper questionnaires included in the PASTOR-plus packet with PASTOR submeasures.

We will compare legacy paper questionnaires completed by study subjects which include the Tampa Kinesiophobia Questionnaire, Patient Activation Measure, Pain Self-Efficacy Questionnaire, Chronic Pain Acceptance Questionnaire and Roland-Morris Disability Questionnaire, and Pain Catastrophizing Scale with PROMIS measures included in the electronic PASTOR assessment, including pain interference, depression, anxiety, anger, and physical function. This will determine if there are legacy questionnaires with prognostic value which should be added to PASTOR.

Analytical Technique: We will use correlation analysis to determine the relationship between legacy paper questionnaires and PASTOR submeasures.

Aim 4: Evaluate the relationship between self-reported physical function (from PASTOR) and clinician-supervised tests of physical function, such as exercise treadmill test at all timepoints.

We will compare self-reported physical function with clinician-supervised tests of physical function to determine if PASTOR respondents over or under-estimate their physical capacity.

Analytical Technique: We will use correlation analysis to explore the relationship between self-report and clinician supervised tests of physical function.

Aim 5: Determine whether outcomes differ between the subgroup of participants who completed FR program 4 days per week x 3 weeks vs 2 days per week x 6 weeks.

During the course of the study, a protocol modification was approved to allow subjects to participate in the FR program with an extended 2 days per week over 6 week schedule with the same number of treatment hours as the original 4 days per week for 3 weeks. We will evaluate outcomes in both groups to determine if one treatment approach yielded superior outcomes to the other.

Analytical Technique: We will use a Sequential Multiple Regression model.[79] We will assess the relative importance of the FR delivery method (either 4 days per week x 3 weeks vs. 2 days per week x 6 weeks controlling for treatment group on our primary outcomes of pain and physical function as well as on the secondary outcomes measures (depression, anxiety, anger, sleep quality, fatigue, medical board status for disability, duration of pain-related disability, prescription opioid dosage, and functional capacity tests for endurance and strength).

Aim 6: Compare outcome measures collected within narrow timelines to those collected within flexible timelines.

We attempted to collect outcome measures at the following timepoints: 1) within one month before starting treatment; 2) within the last day of pre-FR stage through the first day of FR stage; 3) on the last day of FR; 4) 3- and 5) 6- months after the end of FR. However, this precise collection schedule was not always possible. For example, baseline measures were collected more than one month before the start of treatment for study subjects who had conflicts such as military training exercises, personal or family illness or planned leisure travel which postponed the start of study treatment. Collection of follow-up measures was sometimes earlier or later than desired when study subjects with conflicts were unavailable at the time outcomes were requested. We plan to compare outcomes collected within the above timeframes with those collected within timeframes with modest and moderate flexibility as outlined in the following table. This analysis will inform the design of future pragmatic clinical trials in determining acceptable timeline parameters for collection of pain outcomes.

	Baseline	**End of pre-FR stage**	**End of FR stage**	**Short-term**	**Intermediate-term**
Narrow timelines	w/in 1 month of treatment start	Last day of pre-FR up to start of FR	Last day of FR	3 months after end of FR	6 months after end of FR
Modest flexibility	w/in 2 months of treatment start	≤ 2 treatment days before end of pre-FR, through ≤2 treatment days after start of FR	≤ 2 treatment days before end of FR, through ≤ 7 calendar days after end of FR	2-4 months after end of FR	5-7 months after end of FR
Moderate flexibility	w/in 3 months of treatment start thru 2 days after treatment start	≤2 treatment days before end of pre-FR, through ≤4 treatment days after start of FR	≤ 2 treatment days before end of FR, through ≤30 calendar days after end of FR	1-<5 months after end of FR	6-9 months after end of FR

Analytical Technique: We will use a Sequential Multiple Regression model.[79] We will assess the relative importance of the timing of assessments on our primary outcomes of pain and physical function as well as on the secondary outcomes measures (pain interference, depression, anxiety, anger, sleep quality, fatigue, medical board status for disability, duration of pain-related disability, prescription opioid dosage, and functional capacity tests for endurance and strength). We will code an indicator variable to document every observation that occurs within the narrow timeline. We will use an interaction term of this indicator with the intervention to see if the intervention shows a differential effect for those who adhere to the narrow assessment timelines.

Aim 7: **Determine if patient activation, pain catastrophizing, self-efficacy or pain acceptance moderate or mediates pain and function outcomes.**

We will determine if level of patient activation, catastrophizing, self-efficacy and pain acceptance as measured by legacy questionnaires completed by study subjects have an impact on pain and functional outcomes.

Analytical Technique: We will using a multiple linear regression approach to determine the roles of patient activation, pain catastrophizing, self-efficacy, and pain acceptance with regard to the intervention outcomes. Baron and Kenny[86] described mediation and moderation testing and their work has been developed further by methodologists. We will use Hayes' conditional process tools[87] to test if patient activation, pain catastrophizing, self-efficacy, and pain acceptance are affected by the intervention and help explain the outcomes, that is, if they are a mechanism for how the intervention helps people (mediation). We will compare models with and without the mediating variables and partition the total effect of the intervention into indirect effects due to impact on hypothesized mediators and the remaining direct effects. Using interaction terms, we will also examine if these variables may moderate the relationship of the intervention on the outcomes, helping explain who is responding best to the intervention. This approach can be extended to determine if how the intervention works differs by participant characteristics, that is moderated mediation.

12.0 Participant Information

12.1 Subject Population:

Active duty service members with chronic pain

12.2 Age Range:

- [ ] 0-17
- [x] 18-24
- [x] 25-34
- [x] 35-44
- [x] 45-54
- [x] 55-64
- [ ] 65-74
- [ ] 75+

12.3 Gender:

- [x] Male
- [x] Female

12.4 Special categories:

- [ ] Minors /Children - "You must also consider the requirements of 45 CFR 46 Subpart D and DoDI 3216.02, Enclosure 3, paragraph 7.d."
- [ ] Students
- [ ] Employees - Civilian - "You must also consider the requirements of DoDI 3216.02, paragraph 7.e."
- [ ] Employees - Contractor
- [ ] Resident/trainee
- [ ] Cadets /Midshipmen - "You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraphs 7.e. and 12."
- [x] Active Duty Military Personnel - "You must also consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e."
- [x] Wounded Warriors - "Depending on your intended subjects' status, you may also need to consider the requirements of DoDI 3216.02, Enclosure 3, paragraph 7.e."
- [ ] Economically Disadvantaged Persons - "You must also consider the requirements of 32 CFR 219.111 (b)."
- [ ] Educationally Disadvantaged Persons - "You must also consider the requirements of 32 CFR 219.111 (b)."
- [ ] Physically Challenged (Physical challenges include visual and/or auditory impairment)
- [ ] Persons with Impaired Decisional Capacity - "You must also consider the requirements of 10 USC 980."
- [ ] Prisoners - "You must also consider the requirements of 45 CFR 46 Subpart C and DoDI 3216.02, Enclosure 3, paragraphs 7.b. and 7.c."
- [x] Pregnant Women, Fetuses, and Neonates
- [ ] Non-English Speakers
- [ ] International Research involving Foreign Nationals - Headquarters Review is necessary

12.5 Inclusion Criteria:

Order Number	Criteria
1	Significant functional impairment due to pain, requiring modification of military duties.
2	Physically able to participate in up to four hours of physical activity (strength, flexibility, endurance training) per day: 1. Can stand up from and sit down on floor independently 2. Can complete at least 6 minutes of Naughton Treadmill Protocol. . 3. Able to complete at least 2 of the following: -Lift 20 lbs from floor to knuckle height. -Lift 20 lbs from floor to shoulder height. -Carry 20 lbs at least 40 feet.
3	Inadequate response to previous less intensive treatment
4	Expresses motivation to take active role in regaining function

12.6 Exclusion Criteria:

Order Number	Criteria
1	Major surgeries within past 6 months or planned within next 6 months.
2	Unstable psychological disorders

3	Active substance use disorder
4	High dose opioids of ≥90 milligrams of morphine equivalent doses (MED)/day
5	In the Medical Evaluation Board process and without defined availability for any treatment scheduling

13.0 Recruitment and Consent

13.1 Identification and Selection of Subjects:

Subjects will be selected from among the patients referred to the IPMC for whom an IPMC physician recommends participation in FR and who are determined by an IPMC physical therapist to meet minimal standards of physical function required for successfully FR participation.

13.2 Recruitment Process:

Study participants will be recruited from the population of patients who are referred to the Madigan Interdisciplinary Pain Management Center and who are determined by the treating physician to be a candidate for the FR program. If the patient is willing to commit to this intensive treatment approach, he/she will be evaluated by a physical therapist to determine if he/she has the physical stamina to successfully participate in FR. If so, his/her commanding officer will be contacted by a nurse case manager and asked to approve the patient's absence from work as needed for the six-week program. Any patients who receive approval from their commanding officer to participate in FR will be considered for inclusion in the study.

13.3 Compensation for Participation:

No compensation for study

13.4 Eligibility Assessment Process:

A partial HIPAA waiver of authorization will be requested to allow the research coordinator or research assistant to perform a prescreen of medical records of potential subjects to determine if they have any excluding conditions.

13.5 Consent Process:

Are you requesting a waiver or alteration of informed consent?

(•) Yes ( ) No

What type?

☐ Waiver of documentation of informed consent
☑ Waiver or alteration of informed consent

Please explain why you qualify for a waiver or alteration of informed consent:

Waiver is requested to determine if subjects are eligible for participation. Eligible patients interestedin participation will undergo informed consent.

Please explain the consent process:

Following the prescreen process, any potential subjects will meet with the research coordinator or research assistant who will explain the study and request that the patient participate. Patients who express an interest in participating will be consented. Patients who decline to participate in the study will be given the option of proceeding with the integrative modalities program and/or the functional restoration program as recommended by their physician.

Research staff will approach eligible patients during an out-patient IPMC visit or by telephone, explain the study and answer questions about the study (refer to Enrollment Script). If the patient express willingness to participate in the study at the time of this discussion, they will be consented. If eligible patients do not decline participation but request more time to consider participation, the research staff will re-contact them within 1 week of the initial contact to enable them to consent or decline. Eligible patients who decline study participation will be asked to share reasons for refusal., A confidential list of patients who have been approached but who are not enrolled in the study will be maintained by the research staff to ensure that no patient is approached more than once. A HIPAA waiver of authorization is requested for the creation and maintenance of this list, as it poses minimal risk to patient privacy and is essential to ensure that patients do not perceive coercion to participate in the study. The number of eligible patients, those approached, enrolled, and the reasons for refusal, will be recorded.

13.6 DoDI 3216.02 requires an ombudsman to be present during recruitment briefings when research involves greater than minimal risk and recruitment of Service members occurs in a group setting. If applicable, you may nominate an individual to serve as the ombudsman.

- (•) N/A
- ( ) Propose ombudsman

13.7 Withdrawal from Study Participation:

Explain the process for withdrawal and specify whether or not the subjects will be given the opportunity to withdraw their data their data/specimens in the event they wish to withdraw from the study

Participants may elect to discontinuation participation in the study at any time. This decision will not affect their eligibility to continue the integrative modalities program or functional restoration program. If they elect to discontinue participation in the integrative modalities (IM) and/or functional restoration (FR) program, they will be offered other appropriate therapies offered in the IPMC, such as medication management and/or interventional pain therapies. On rare occasions patients in the IM program or FR program are disenrolled from the program by the clinical team. Reasons include repetitive missed appointments and/or behavior that is disruptive to the treatment group. Patients demonstrating these behaviors are counseled and given the opportunity to engage more effectively in treatment prior to disenrollment.

14.0 Risks and Benefits

14.1 Risks of Harm:

Identify all research-related risks of harm to which the subject will be exposed for each research procedure or intervention as a result of participation in this study. Consider the risks of breach of confidentiality, psychological, legal, social, and economic risks as well as physical risks. Do not describe risks from standard care procedures; only describe risks from procedures done for research purposes

Risks: Participation in this research study will involve treatment with physical and occupational therapy, acupuncture, chiropractic, yoga with or without medical massage and biofeedback. All of these modalities are low risk treatments, and these risks will be explained to potential subjects during the informed consent process.

Psychological distress: It is possible that some participants will experience psychological distress during pain therapies. This risk will be mitigated by attempting to make the therapies as comfortable as possible for each participant. It is not anticipated, but in the event any psychological/emotional distress occurs, the PI will stop the therapy, and soothe, calm, and assist the participant in regaining control before the therapy continues. In the event that this is not effective, the PI will refer the participant to the appropriate primary care provider or a health care professional at Madigan Army Medical Center.

Loss of Confidentiality: This risk will be mitigated using several precautions discussed in Confidentiality of Research Data.

14.2
Measures to Minimize Risks of Harm (Precautions, safeguards):

For each research procedure or intervention, describe all measures to minimize and/or eliminate risk of harms to subjects and study personnel

The therapeutic approach to treatment modalities will be adjusted as needed based on each patient's response to therapy. For example, if one chiropractic technique increases pain, other techniques will be employed to improve response. While mild muscle soreness is common in FR programs, it is unlikely that injury will occur. If acute injuries do occur, the patients will be managed by IPMC medical staff or their primary care team within MAMC at no cost to the study participant.

This risk of psychological distress will be mitigated by attempting to make the therapies as comfortable as possible for each participant. It is not anticipated, but in the event any psychological/emotional distress occurs, the PI will stop the therapy, and soothe, calm, and assist the participant in regaining control before the therapy continues. In the event that this is not effective, the PI will refer the participant to the appropriate primary care provider or a health care professional at Madigan Army Medical Center.

The risk of loss of confidentiality will be mitigated using several precautions discussed in Confidentiality of Research Data.

14.3
Confidentiality Protections (for research records, data and/or specimens):

Describe in detail the plan to maintain confidentiality of the research data, specimens, and records throughout the study and at its conclusion (e.g., destruction, long term storage, or banking). Explain the plan for securing the data (e.g., use of passwords, encryption, secure servers, firewalls, and other appropriate methods). If data will be shared electronically with other team members/collaborators outside the institution, describe the method of transmission and safeguards to maintain confidentiality. Explain whether this study may collect information that State or Federal law requires to be reported to other officials or ethically requires action, e.g., child or spouse abuse

Confidentiality of the Data.
Complete confidentiality cannot be promised, particularly for military personnel, because information bearing on health or illegal activities may be required to be reported to appropriate medical or command authorities.

The research records may be looked at by staff from Madigan Army Medical Center's Department of Clinical Investigation and the Institutional Review Boards (IRB) of Madigan Army Medical Center. The records may be looked at by staff from the Army Clinical Investigation Regulatory Office (CIRO), Army Human Research Protections Office (AHRPO), the study sponsor, and other government agencies that provide oversight for human subject protection as part of their duties.

All identifying information will be excluded and/or removed from study documents to the greatest extent possible. Each individual screened for participation will be assigned a unique study identification number. The study identification number links the individual to study documents and will be used to

help prevent disclosure of identifiable personal information. Study identification numbers will be maintained by the PI on a master list that will be stored separately from other study documents in a locked cabinet.

Study documents will be stored in locked cabinets and on secure servers. Study documents in use will be managed on password protected computers with password protected storage devices with documents and files that do not contain identifiers.

Database and master list will be stored on a password protected secure computer in the research coordinator's office. Master list will also be stored on password protected Excel spreadsheet, accessible only to research coordinator, research assistant and PI. Master list will not leave Madigan. The de-identified data will only be shared among the PI, AI, and the collaborators of this study. Only the PI, research coordinator, research assistant, and clinical staff involved in study visits will have access to forms containing PHI, these forms will be stored in a locked file cabinet in the research office and will not leave Madigan. PASTOR Data will be kept on a secure server. All data will be de-identified before being transferred to an electronic database at the University of Washington, on the 14th floor of the Health Sciences Building for analysis. Data will be transferred via secure methods, and subject data will not be linked to other databases. Only authorized persons actively involved in conducting the study, monitoring safety and evaluating study results will have access to the records.

The following data types will be compiled by the Defense Health Agency Clinical Support Programs Solution Delivery Division (DHA/SDD) through an approved data sharing agreement. The process for data management and de-identification of these data is explained in the data management section.

- Demographic information for study subjects
- Prescription data
- Opioid dosage and associated risk of serious respiratory depression as reported in the Defense Health Agency Opioid Registry
- Military medical readiness as reported in the Army Medical Protection System (MEDPROS)
- Number of clinical encounters and number and type of interventional procedures which each subject underwent in the Madigan Interdisciplinary Pain Management Center during the study period
- Diagnosis codes

Once data collection is complete, the master list will be destroyed.

The PI will manage, maintain, and secure all study documents and materials. The PI as the primary control point, combined with a small supporting research team, will help protect against disclosure.

14.4 Potential Benefits:

Describe any real and potential benefits of the research to the subject and any potential benefits to a specific community or society

If the individuals in the research are considered experimental subjects (per 10 USC 980), and they cannot provide their own consent, the protocol must describe the intent to directly benefit all subjects

For us as a nation to continue achieving health care advances that enhance the health of military service members and promote a fit and ready force, it is important that service members be able to participate in ethically sound research. These health advances are also important for society in general. Military health care research is often found to be relevant to civilian health care, particularly in the management of pain and trauma. The potential benefits of participation in these treatment modalities include pain relief, improved functional improvements and improved mood. As the risks for the proposed study are minimal, the potential benefits outweigh the risks.

14.5 Privacy for Subjects:

Describe the measures to protect subject's privacy during recruitment, the consent process, and all research activities, etc.

Prospective study subjects will be informed about the study in a private area of the clinic or by telephone from the research staff office. A Request for Partial Waiver of HIPAA Authorization for Recruitment will be requested to permit the research assistant or research coordinator to review potential subjects' medical records to ensure there are no disqualifying conditions, such as impending surgery or unstable psychological status. This review of medical records is required for all FR participants, regardless of study participation status. Baseline and outcomes data that will be collected from study participants are the same data that are collected from all IPMC patients who participate in the functional restoration (FR) program, regardless of status of research project participation and are used to guide therapy. The IPMC has been using these or similar measures since the FR program started in 2013. Measures to ensure confidentiality are discussed in section 7.3.3.

14.6 Incidental or Unexpected Findings:

Describe the plan to address incidental findings and unexpected findings about individuals from screening to the end of the subject's participation in the research. In cases where the subject could possibly benefit medically or otherwise from the information, state whether or not the results of screening, research participation, research tests, etc., will be shared with subjects or their primary care provider. State whether the researcher is obligated or mandated to report results to appropriate military or civilian authorities and explain the potential impact on the subject

The study is low-risk; therefore we do not anticipate any serious adverse events.

The most likely adverse event associated with participation in this study is mild-self-limited muscular soreness in the initial days of functional restoration, as each participant begins the reconditioning process. This is anticipated to occur in 75% of participants and to resolve within one week of onset. These complaints will be addressed and managed by the IPMC physical and occupational therapy teams.

This intervention qualifies as a Phase II clinical trial. We have developed a data and safety monitoring plan, which is outlined below. The plan includes routine monitoring of adverse events by the PI and study staff.

Monitoring study safety. Study safety will be monitored quarterly and includes auditing a random selection of 5% of cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents and investigator compliance. Conference calls or in-person meetings are scheduled quarterly or on an as-needed basis with all data collectors and providers to review protocol and possible study safety issues. Booster sessions on administering the protocols will be given if needed. Each study team member will also receive a personal performance update with comments on protocol adherence and completeness of data. All violations of protocol are noted.

Identification of Adverse Events. Dr. Flynn will be responsible for monitoring the internal review of adverse events. Adverse events will be identified by either intervention facilitators or study staff and reported to either Dr. Flynn within 72 hours of occurrence, who will determine whether the event qualifies for reporting to the IRB.

To help ensure consistency in reporting, adverse events and safety alerts will be tracked using a standardized form that records the date of the event, attribution of the event (e.g., intervention-related or external situation, such as a death in the family), resolution of the event (whether resolved or controlled), and date of resolution.

The format of the form was validated during our previous work and is shown in Table 1.

Table 1: Adverse Event Reporting Form with Sample Text Entries

Event	Date	Severity	Attribution	Operational definition	Resolution

Sample entry:					
Suicidal behavior	XXX	Serious	Not intervention-related/ assessed at baseline	Any risk or attempt to inflict serious bodily harm to self that may result in death	-Referral to mental health practitioner -Event is ultimately resolved when the mental health practitioner determines that there is no further risk

In handling adverse events, project staff will follow the general principles devised for developing a safety plan for behavioral trials. Namely:

1. Adverse events queries should include domains plausibly affected by the interventions being tested. A primary question in defining adverse events in behavioral trials pertains to potential risks or negative events that can occur as a result of a specific intervention or of study procedures. Behavioral intervention research needs to also address behavioral, psychological, legal, economic, and social events, as these domains could be affected by the intervention being tested. To understand the adverse events or unexpected problems that can occur as a result of a behavioral intervention, it is important to monitor what the process of change will entail. These changes can be inherent to the mechanism of action of intervention under study. For example, addressing one's fears or challenging false beliefs may increase the risk of suicidal thoughts or behavior. The research team will keep detailed field notes about each visit and phone call.
2. Monitoring should attempt to assess relationships between intervention and adverse events.
3. Systematic monitoring is essential to identifying unexpected events. In addition to immediately addressing a potential adverse event, the research team will discuss all active cases in depth during the weekly research team meetings, and any potential adverse events, safety alerts, or other concerns will also be discussed.
4. Effective monitoring is a shared responsibility that includes multiple stakeholders, namely the research team, the Advisory Committee, and the IRBs.

All events will be discussed on a monthly basis during research team meetings, and any adjustments to the intervention or study protocol will be negotiated and agreed upon by the team.

15.0 Study Monitoring

15.1 Data Monitoring Plan:

Describe the plan to monitor the data to verify that data are collected and analyzed as specified in the protocol. Include who will conduct the monitoring, what will be monitored and the frequency of monitoring

Study safety will be monitored quarterly and includes auditing a random selection of 5% of cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents and investigator compliance. Conference calls or in-person meetings are scheduled quarterly or on an as-needed basis with all data collectors and providers to review protocol and possible study safety issues. Booster sessions on administering the protocols will be given if needed. Each study team member will also receive a personal performance update with comments on protocol adherence and completeness of data. All violations of protocol are noted.

15.2 Safety Monitoring Plan:

Describe the plan to monitor the data to ensure the safety of subjects

Study safety will be monitored quarterly and includes auditing a random selection of 5% of cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents and investigator compliance. Conference calls or in-person meetings are scheduled quarterly or on an as-needed basis with all data collectors and providers to review protocol and possible study safety issues. Booster sessions on administering the protocols will be given if needed. Each study team member will also receive a personal performance update with comments on protocol adherence and completeness of data. All violations of protocol are noted.

15.3 Does your study require independent data and safety monitoring?

○ Yes ◉ No

16.0 Reportable Events

16.1 Reportable Events:

Consult with the research office at your institution to ensure requirements are met
• Describe plans for reporting expected adverse events. Identify what the expected adverse events will be for this study, describe the likelihood (frequency, severity, reversibility, short term management and any long term implications of each expected event)
• Describe plans for reporting unexpected adverse events and unanticipated problems. Address how unexpected adverse events will be identified, who will report, how often adverse events and unanticipated problems will be reviewed to determine if any changes to the research protocol or consent form are needed and the scale that will be used to grade the severity of the adverse event

All unanticipated problems involving risk to subjects or others and all serious adverse events or subject deaths related to the research will be reported within 48 hours of the research team's knowledge of the event to the MTF IRB. Submission of a complete written report in IRBNet will follow the initial notification within 10 working days.

17.0 Equipment/non-FDA Regulated Devices

17.1 Does the study involve the use of any unique non-medical devices/equipment?

○ Yes ◉ No

18.0 FDA-Regulated Products

18.1 Will any drugs , dietary supplements, biologics, or devices be utilized in this study?

☐ Drugs
☐ Dietary Supplements
☐ Biologics
☐ Devices
☑ N/A

18.5 Sponsor (organization/institution/company):

☑ N/A

If applicable, provide sponsor contact information:

19.0 Research Registration Requirements

19.1 ClinicalTrials.gov Registration:

◉ Registration is not required
○ Registration pending
○ Registration complete

19.2 Defense Technical Information Center Registration (Optional):

◉ Registration is not required
○ Registration pending
○ Registration complete

20.0 References and Glossary

20.1 References:

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20.2 Abbreviations and Acronyms:

AAG – Army Analytics Group

DHA – Defense Health Agency

EIDS – Enterprise Intelligence and Data Solutions

IPMC – Interdisciplinary Pain Management Center

M2 – Military Health System Mart

MAMC – Madigan Army Medical Center

MODS – Military Operational Data Systems

REACH program – **Re**stor**A**tion through **C**omplementary and Integrative **H**ealth – interdisciplinary program comprised of twice weekly chiropractic, acupuncture, yoga, massage and health psychology

SCOUT program – **S**tandard **C**are **OUT**patient program - interdisciplinary program comprised of twice weekly physical therapy, occupational therapy and health psychology

SDD – Solution Delivery Division

UW – University of Washington

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MCHJ-CLI 17 January 2018

MEMORANDUM FOR DIANE MCFADDEN FLYNN, MD - Madigan Army Medical Center (MAMC)

SUBJECT: RHC-P IRB Office Acknowledgement of Research Project "Enhancing the Success of Functional Restoration Using Integrative Therapies: Comparative Effectiveness Analysis in Active Duty Service Members With Chronic Pain"

PROTOCOL #215050

1. The subject EIRB protocol application has been reviewed by the Regional Health Command-Pacific IRB Support Office.

2. This project retains the expiration date of 25 April 2018. In accordance with 32 CFR 219.109(e) the project must be reviewed for continuation by the RHC-P IRB by this expiration date; reminders will be sent at 90, 60 and 30 days prior to this date.

3. The IRB point of contact for this review is the undersigned; 253-968-3524 or Athena.m.rayner.civ@mail.mil.

Athena Rayner
IRB Manager
Regional Health Command-Pacific IRB