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Official Study Title: Establishing Efficacy of a Functional Restoration-Based CAM Pain Management Program in a Combat Injured Veterans Population

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Establishing Efficacy of a Functional Restoration-Based CAM Pain Management Program in a Combat Injured Veterans Population

A randomized clinical trial of an interdisciplinary program with a strong CAM component (the FORT-A Program) to address chronic pain management and persistent opioid use in a sample of 130 OEF/OIF/OND Veterans with polymorbid chronic musculoskeletal pain

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Tool Revision History

Version Number: 1.0 Version Date: 17 JUL 2014
Revision Summary: N/A (New Protocol)

Version Number: 2.0 Version Date: 03 OCT 2014
Revision Summary: Added information on VA Opioid Safety Initiative
Inclusion of some regulatory procedures based on VA R&D Review for this study (occurred Oct 2, 2014)

Version Number: 3.0 Version Date: 11 NOV 2014
Revision Summary: Added STRONG STAR SOPs and integrated study operations with STRONG STAR regulatory infrastructure

Version Number: 4.0 Version Date: 13 JAN 2015
Revision Summary: Added information about the qualifications of treatment providers for group and individual treatments (Sec 5.2); Revised and clarified randomization blocking after consultation with Dr. Li (Sec 4.3 & 6.2.2); Added a table of interventions received in PRC Usual Care (Sec 5.1); Clarified Physical Therapy in the Treatment as Usual Group (Sec 5.1.1); Provided a list of prohibited interventions (Section 5.3.3); Added descriptions of endpoints being used in the study (Sec 9.5.1& 9.5.2); Clarified ITT population (Sec 9.3); Added detail to plan for minimizing and managing missing data (Sec 9.6); Clarified analytic strategy at Mo. 12 (Sec 9.6).

Version Number: 5.0 Version Date: 08 JUNE 2015
Revision Summary: Added Co-Coordinator to Figure 2 (Page 18); Clarified Role of Co-Coordinator throughout (Various Sections); Added Specific Names for the IE and Fellow in Figure 2 (Page 18); Adjustment to Inclusion and Exclusion Criteria (Sec 4.1); Clarification on PT referral through PRC (Sec 4.1 and 5.1.1); Added PRC PT/OT personnel (Sec 5.2 and 7.1); Added STRONG STAR Interns as study providers (Sec 5.2, Figure 2); Clarification on Exclusion for impaired cognition (Sec 4.2); Amended “enrollment” and ensured assessment windows reference this definition (Sec 6.2.2, 6.2); Changes to Measures s/p Westat visit and STRONG STAR Assessment Core (MINI only given in screening Section 6.1; Change from Actical to Actiwatch Sec 6.2.4, 6.2.5, 9.5.2; Change from BDI-2 to PHQ-9 Section 6.2, 7.3; Extension of Assessment Windows (Sec 6.1); Clarified assessment windows per STRONG STAR Standard Operating Procedure; Removed reference to “quarterly” NCCIH reviews (Sec 10.3.4 and 10.3.5); Add pregnancy test at screening (Sec 6.2.1).

Version Number 6.0 Version Date: 14 OCT 2015
Revision Summary: Added a summary of changes for this Amendment (Page 4). Updated Precis to fit new opioid criteria and outcomes (PRECIS). Updated background to include information about opioid withdrawal and recidivism (Sec 2.1). Added information about definition of opioid recidivism as well as outcomes assessment for opioid and other pain medication changes in study design (Sec 3). Changed inclusion criterion for opioid use to include persistent opioid users *or* previous opioid users who were discharged off of opioid medications through the OSI (Sec 4.1). Updated exclusion criteria and prohibited treatments to include veterans enrolled in naloxone-based treatment for opioid dependence (Sec 4.2 & 5.3.3). Added information to the

section on the OSI as justification for inclusion change (Sec 5.3.4). Updated Precis with new opioid criteria. Updated study objectives with new opioid objectives (Sec 1.1). Added an explanation of OSI inclusion in study rationale (Sec 2.2). SOWS to be given at baseline (Sec 6.1). Updated opioid hypothesis (Sec 9.1). Updated opioid data methods (Sec 9.5.2). Added info about screening for OSI referral (Sec 6.2). Added opioid assessments in CPRS/PAT and Medication Quantification Scale III (Sec 6.1, 6.2.2, 6.2.4 & 6.2.5). Updated Section 7 to reflect weekly phone call / meeting and updated justification for opioid safety monitoring (Sec 7.2 &7.3). Updated design issues for opioid hypothesis (Sec 9.1). Updated sample size justification to emphasis powering to Aim 1 despite the change to Aim 2 (Sec 9.2). Updated data analytic strategy for opioid medication (including sample size justification; Sec 9.2 & 9.6). Updated secondary outcome description for opioid and other pain medications (Sec 9.5.2). Added references (Sec 14).

Version 7.0 Version Date: 19 APR 2016
Revision Summary: Addition of new measures to assessment battery as Common Data Elements of the STRONG STAR Research Consortium (these measures were recently added in all Consortium and Affiliate trials) including measures of tobacco (Fagerstrom Test for Nicotine Dependence-FTNB; Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco (FTND-ST), Quick Drinking Scale. New measures were added to Sections 6.1, 6.2.2, and 6.2.4. The name of the Medical History Interview has been changed to Health Questionnaire/Addendum in Sections 6.1 and 6.2.2. Inclusion criterion for depression in Section 4.1 was changed to reflect assessment with the PHQ-9 instead of the BDI-2 (this change was missed when we previously amended the protocol to replace the BDI-2 with the PHQ-9 to be consistent with other STRONG STAR and Affiliate studies). Broadened opioid Inclusion Criterion #6 to read “on their own or by a provider during the OSI period.”

Version 8.0 Version Date: 18 JULY 2017
Revision Summary: Gulf War era Veterans are now eligible to participate in addition to Operations Iraqi Freedom (OIF), Enduring Freedom (OEF), or New Dawn (OND) era Veterans.

Version 9.0 Version Date: 26 November 2018
Revision Summary: Under Section 5, Study Interventions we added that individual sessions (depression, PTSD) may be conducted by other clinic providers if subject is already engaged in treatment prior to enrollment. If sessions are conducted by another provider, the quality of care will be standard clinical care which is appropriate for this protocol; however, the duration of care may be variable so we will be tracking number of sessions attended. For those subjects receiving Individual sessions from another clinic provider, the 15 minute pain management session will be included with their biofeedback session. Because we are not allowed to ask them to discontinue VA intervention and it is unethical to over-treat another mental health provider (per APA and Texas State Board rules), we cannot provide individual sessions to those participants.

Revised the inclusion criteria to specify that participants need to have no opioid use for one week before the pain management program period (weeks 1-3). The original criterion of being discharged off of persistent opioid medications during the OSI period was used because of the decrease in opioid prescriptions in the VA under the opioid safety initiative (such that most

participants were going to be discontinued on opioid medications and we wanted a homogenous sample). It must be noted that up to 40% of pain sufferers who try to discontinue opioid medications (after persistent use) will fail to discontinue. The PI has noted that the investigational intervention, because of its capacity to lead to decreased need for medications (including and especially opioids for pain management) through improved non-pharmacological pain management training, is likely to be helpful for veterans who both successfully and unsuccessfully discontinue opioids. Thus, this change was made to maximize benefit of the intervention in the VA population without sacrificing scientific rigor.

Version 10.0 Version Date: 9 September 2019
Revision Summary: Addition of a new measure to capture data from participants who were lost to contact or dropped from treatment. The Missing Data Assessment is a 4-item measure of global symptom improvement of pain, perception of satisfaction and burdensomeness of study treatments, and reason(s) for discontinuing study participation. This assessment will be used to assess missing data randomness and to categorize participants who discontinued study participation as a way to help impute missing data and improve future studies with these treatments in similar populations. In addition to the Missing Data Assessment, participants who withdrew from the study will also be contacted to complete the ODI, TLFB and Concomitant Meds Form.

Summary and Justification for Amendment 6 Changes

Amendment 6 of this document includes an unusual revision of a Study Aim (Aim 2). In this case, Aim 2 of this protocol is being revised in response to external events that threaten the feasibility of the originally proposed research and the clinical utility of the Aim 2 findings. Because of the scope of change, this summary was developed to provide an explanation and context for why/how this decision was made. To save space, the reader is encouraged to review the changes made throughout the document as described in the Version 6.0 Revision Summary on the previous page. This study was originally proposed as a test of functional restoration rehabilitation (with a mindfulness content core) in addressing service-related chronic pain among post-9/11 deployment era veterans. In so doing, the investigators developed a secondary aim to address the important question of opioid use for pain management in the VA and the effect of functional restoration on opioid sparing. After this proposal was submitted to NCCIH for funding determination, the Department of Veterans Affairs began to implement an Opioid Safety Initiative (OSI; see Section 5.3.4 for a thorough description and updates) that resulted in a significant shift in opioid prescription patterns in the VA. The South Texas Veterans Health Care System was identified as a "Top 10 Performer" in the OSI in August 2015, and a significant number of persistent opioid users in this VA system are no longer using opioid medications.

Changes under the OSI posed two challenges to this research and the VA system as follows:

1) As this research program progresses, there will be fewer veterans meeting "persistent opioid use" inclusion criteria over time; a threat to feasibility of recruitment and exemplary of how the population of interest (veterans with polymorbid pain) is likely to change over the course of this study. In order to meet the needs of the population, this research needs to adjust Aim 2 to better exemplify Veterans who are *prior* opioid users versus current persistent users. Because the VA has already implemented an administrative protocol to decrease opioid prescriptions given to patients, maintaining a clinical aim of opioid sparing after functional restoration treatment makes no sense. The new question is: Can the VA keep veterans from returning to opioid use?
2) The OSI requires the VA to develop an alternative intervention strategy for veterans in pain who discontinue opioid medications, with an emphasis on CAM. In discussions with the STVHCS OSI (as recently as October 14, 2015), the PI and study team have confirmed that the proposed study would meet the VA's needs if the pain program addresses *return to opioid use (e.g., opioid recidivism)* instead of opioid sparing. Making this change would doubly benefit the VA as a referral outlet for alternative pain management and a data-gathering mechanism to help them assess progress. Win-win.

This protocol has made several Aim 2 changes to make the most of this opportunity including: changing the Aim 2 endpoint to opioid recidivism (i.e., using an opioid medication 3+ days in a 30 day period), adapting the MEMS caps to assess other pain medication patterns that may shift after veterans stop opioids, using the Medication Quantification Scale to capture the change in medication safety over time, and increased frequency of medication assessment to powerfully assess Aim 2 with this sample size. It is important to note that this study *must be powered to address Aim 1* because improved pain management is the most likely vehicle for decreasing opioid recidivism over time. However, increased frequency of medication assessment does provide sufficient power to detect differential rates of recidivism between FORT-A and TAU.

TABLE OF CONTENTS

Page

Study Title

Establishing Efficacy of a Functional Restoration-Based CAM Pain Management Program in a Combat Injured Veterans Population

Objectives

AIM 1: Assess the efficacy of the FORT-A Program for improved pain management outcomes in (N=130) polymorbid OEF/OIF/OND Polytrauma Rehabilitation Center (PRC) Veterans with chronic musculoskeletal pain (CMP) using a 1:1 randomized clinical trial comparing FORT-A to standard PRC care. We will determine the improvement in pain management outcomes attributable to a fully integrated and manualized interdisciplinary pain program (FORT-A) compared to standard PRC care.

AIM 2: Assess the efficacy of FORT-A for decreasing the rate of opioid recidivism (using any opioid for 3 or more days in any 30-day period) compared to standard PRC care in a sample of OEF/OIF/OND polymorbid CMP Veterans discharged off of opioid medication in VA care since the start of the OSI. Unlike the original FORT trial, this research will formally and prospectively track opioid medication use among polymorbid Veterans to sensitively detect changes in chronic opioid therapy attributable to FORT-A versus PRC treatment. FORT-A is expected to produce significant reductions in the rate of opioid recidivism by imparting numerous strategies to supplant opioid medication as a pain management strategy. FORT-A will avoid the stigma of "traditional" opioid abuse treatment and provide a pain management alternative to those who have been discharged from opioid medications as part of the OSI.

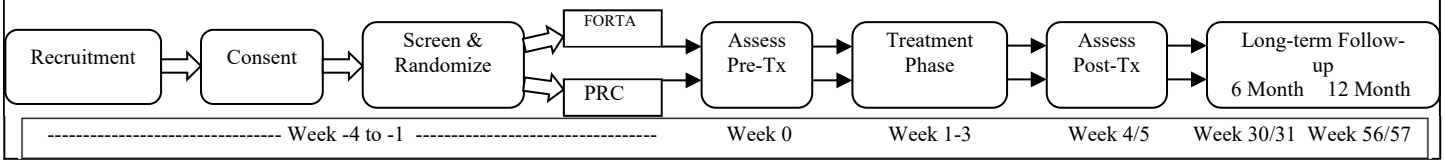
EXPLORATORY AIM 3: Based on the PI's ongoing ESCAPE trial, this research team has identified psychological processes (helplessness, perceived burdensomeness) that likely play a mechanistic role in pain management among OEF/OIF/OND deployers. We will assess these constructs twice a week and analyze latent changes in FORT-A and PRC Veterans to ascertain their role as pain management mediators

Design and Outcomes

This study is a 1:1 block randomized clinical trial comparing the FORT-A program to treatment as usual for polytrauma OEF/OIF/OND Veterans with prior persistent opioid use and chronic musculoskeletal pain who are eligible for treatment through the STVHCS Polytrauma Rehabilitation Center. All participants will be offered Physical Therapy services before enrollment and will be enrolled after completing or denying Physical Therapy (up to 12 sessions as recommended by a PRC Physical Medicine & Rehabilitation Physician (Dr. Eapen, Dr. Jaramillo). If they have already completed PRC Physical Therapy before study enrollment, they will not need to do so again. Also, if the Veteran qualifies but refuses PRC Physical Therapy, he or she will still be eligible to enroll in this study and will not be asked to complete PRC PT. Veterans randomized to PRC (treatment as usual) will then meet with PRC and other VA medical providers per usual standards of care (described below). Those

randomized to FORT-A will complete the standardized FORT-A Program (described in detail below). All participants will complete a standardized battery of assessments at pre-treatment (Week 0), post-treatment (Week 4/5), 6-month follow-up (Week 30/31) and 12-month follow-up (Week 56/57; see Figure 1, below).

Figure 1. Study Activity Flowchart.



Interventions and Duration

FORT-A: An amended version of the military Functional Orthopedic Rehabilitation Treatment (FORT) program. For FORT-A, CBT components of FORT were diminished and replaced with mindfulness and Acceptance and Commitment Therapy (ACT) components. Individual FORT treatment sessions have been altered in FORT-A to focus on PTSD symptom management using an abbreviated, manualized Prolonged Exposure treatment. FORT-A includes:

- 12 sessions (90-minutes each) of manualized group pain management
- 12 sessions (90-minutes each) of group-based functional restoration Physical Therapy
- 6 sessions (75 minutes each) of individual psychotherapy for pain and PTSD
- 6 sessions (30 minutes each) of biofeedback for pain management
- Weekly interdisciplinary case staffings

PRC: The STVHCS PRC is the only self-contained PRC in the VA's nationwide Polytrauma System of Care. The PRC is an interdisciplinary treatment center including: interdisciplinary assessment and treatment, case management, mental health support, physical medicine and rehabilitation (PM&R), physical therapy, speech therapy, prosthetists/orthotists, and other integrated specialty services. The PRC sees approximately 30 new patients each month, most of whom (80%) present with a chronic service-related musculoskeletal pain condition and military trauma comorbidity (traumatic brain injury [TBI], PTSD, depression). Though individual treatment plans may vary, most PRC Veterans will complete up to 12 sessions of Physical Therapy and be followed by a PM&R physician for pain and other symptom management. Pain management with PM&R may include medications, injections, and other palliative medical interventions. The PM&R physicians may also make recommendations about physical function, health behaviors, and mobility.

Sample Size and Population

This research study will include 130 OEF/OIF/OND Veterans who meet the following criteria:

- Present with an ongoing chronic musculoskeletal condition (pain that has been a problem for more than half the days over the past three months) documented in the CPRS record or confirmed by a PM&R physician upon referral to the PRC
- Display at least moderate disability based on an Oswestry Disability Index score

of 20% or greater
- Primary pain complaint was acquired or exacerbated due to military service or a deployment-related injury
- Chronic musculoskeletal pain presents in the context of comorbid psychiatric trauma condition(s) including: mild TBI, PTSD, and/or depression
- Present with a history of persistent opioid use (using opioid medication for 20 out of every 30 days over the past three or more months) and discontinued from opioid medications at the request of their VA provider (e.g., as part of the VA Opioid Safety Initiative [OSI]).
- Speak and read English proficiently
- Eligible to become or are currently enrolled as a STVHCS PRC patient

1. STUDY OBJECTIVES

1.1 Primary Objectives

Hypothesis 1: FORT-A will result in significantly greater improvements in pain management among PRC Veterans compared to standard PRC care based on the primary outcome measure of self-report disability (Oswestry Disability Index) at both short- (pre- to post-treatment) and long-term (6/12-month) follow-up.

Hypothesis 2: FORT-A will also result in significant improvements on secondary pain management outcomes compared to PRC, including pain coping (intensity/ cognitions), emotional distress (depression, PTSD, anxiety), and objective disability (functional capacity, gait) at short- and long-term follow-up.

Hypothesis 3: We hypothesize that FORT-A will result in significantly lower rates of opioid recidivism compared to standard PRC treatment based on timeline followback interview at 12-months follow-up.

Hypothesis 4: We also hypothesize that FORT-A will result in significantly less opioid recidivism compared to PRC treatment based on secondary measures of opioid medications including Medication Event Monitoring System (MEMS), pill counts, and consultation with prescribing providers/ documentation in the VA Electronic Health Record (CPRS).

1.2 Secondary Objectives

Based on the PI's ongoing ESCAPE trial, this research team has identified psychological processes (helplessness, perceived burdensomeness) that likely play a mechanistic role in pain management among OEF/OIF/OND deployers. We will assess these constructs twice a week and analyze latent changes in FORT-A and PRC Veterans to ascertain their role as pain management mediators.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Military operations in Iraq (Operation Iraqi Freedom, OIF) and Afghanistan (Operation Enduring Freedom, OEF; Operation New Dawn, OND) have now lasted for more than a decade, and even as the war effort begins to draw down it is quite likely that the Department of Defense (DoD) and the Veterans Health Administration (VHA) will be confronted with the consequences of OEF/OIF/OND for years to come. Military service members and Veterans who served in OEF/OIF/OND are at increased risk for debilitating chronic pain, with nearly 50% reporting postdeployment pain (Cohen et al., 2005). Our research group has previously published on the significant impact that military chronic pain conditions have on disability in military personnel, active duty retention rates, costs associated with early discharge, healthcare utilization, and long-term disability (McGeary et al., 2012; McGeary et al., 2013; USGAO, 2006). These consequences are costly. The DoD pays an estimated $1.5 billion per year in benefits to disabled services members, approximately 45% of which is accounted for by disability related to chronic pain (Berkowitz et al., 1999; Fabrizio, 2002; Hauret et al., 2010; Belmont et al., 2010). The mechanisms and circumstances of pain onset associated with combating the war on terrorism are unique (e.g., extended use of body armor, turbulent air and ground transport, improvised explosive devices, blast injury), and have made OEF/OIF/OND Veterans increasingly likely to present with chronic pain conditions in the context of psychiatric trauma symptoms (posttraumatic stress disorder/traumatic brain injury; Gironda et al., 2009; McGeary et al., 2011). This comorbidity is often referred to as "polymorbid pain," which many believe is more complex and difficult to treat than non-traumatic pain (Lew et al., 2009; Clark, 2002). Polymorbid pain has presented significant challenges to the DoD and VHA healthcare systems, and there are significant gaps in chronic pain management that must be addressed to ensure best treatment for Veterans with polymorbid pain.

Advancements in military combat casualty care and medical transport have contributed to increased survivability from battlefield injury (cf Belmont et al., 2010). Injured soldiers who may previously have died from a traumatic injury are now surviving with chronic pain and psychiatric trauma symptoms. These symptoms often lead to early discharge from military service, so the significant costs associated with long-term pain management are being passed from DoD military treatment facilities to the VHA (which is likely to serve these chronic pain Veterans for decades). Prevalence rates of chronic pain are as high as 50% in some military Veteran samples (Maloney & McIntosh, 2001), and Veterans with combat trauma conditions (PTSD and/or TBI) are most likely to develop a chronic pain condition 10. Veterans with polymorbid chronic pain are at increased risk for depression (Maloney & McIntosh, 2001), sleep difficulties (Chapman et al., 2006), PTSD (McGeary et al., 2011; Beckham et al., 1997; Otis et al., 2010), anger (Lombardo et al., 2005; Trost et al., 2012), substance abuse (Becker et al., 2009; Goebel et al., 2011), and suicide (Kanzler et al., 2012). The DoD and VHA medical systems are working to address the complexity of polymorbid pain, but our research group has published a description of the significant challenges in treating this population (Lew et al., 2009). There are numerous gaps in VHA health care continuity that contribute to inadequate care or even iatrogenic symptom worsening due to inconsistencies in diagnosis (Reisinger et al., 2012; Roth & Spencer, 2013), with about 45% of polymorbid Veterans treated for post-deployment conditions being currently unemployed in part due to their polymorbid pain (Cohen et al., 2012). Indeed, the Congressional

Budget Office found that VHA treatment costs are 4-6 times higher for polymorbid pain compared to any trauma condition alone (CBO, 2012).

One-dimensional chronic pain management (i.e., medication, physical therapy alone) has failed to adequately meet the needs of this population, and more complex integrated treatment approaches are needed to improve outcomes (Gironda et al., 2009; McGeary et al., 2011). Unfortunately, most Veterans with polymorbid pain are treated with basic medical management. Opioid medications are the most frequently utilized pain management tool for Veterans with chronic pain (Dobscha et al., 2013), and long-term opioid use has consistently shown low efficacy in the rehabilitation of pain, the potential for abuse and dependency, and the potential for worsening pain perceptions (Dobscha et al., 2013; Varney & Bebarta, 2013). A medical record review of 762 OEF/OIF Veterans treated for chronic pain in VA ambulatory clinics revealed that 64% received at least one opioid prescription during a 12 month period and 41% received long-term opioid prescriptions (Macey et al., 2011). Our own research has shown that opioid medications are the most commonly prescribed medication overall in the Veterans Integrated Service Network covering the San Antonio area (VISN 17), and over 40% of Veterans prescribed opioid medications take them for more than 3 months (defined as "chronic opioid therapy"). The risks associated with chronic opioid therapy are undeniable, especially for polymorbid Veterans who are most likely to use opioid medications long term Howe & Sullivan, 2013; Dobscha et al., 2013). These Veterans have an increased likelihood (32%) of receiving benzodiazepine medication concurrently with opioid prescriptions, which promotes risk of overdose-related deaths (Morasco et al., 2010), and they are likely to use opioid medications for non-medical reasons, abuse opioids, and experience increased disability due to poor pain management (Barry et al., 2011; Becker et al., 2008). Surprisingly, few Veterans (25.7%) are ever screened for opioids despite their high rates of opioid use (Morasco et al., 2010).

Both the VHA and DoD have called for effective ways to address high rates of opioid use for OEF/OIF/OND Veterans with chronic pain. Although there are efficacious options for treating opioid dependence and chronic opioid use, there is reason to believe that these options are less effective than intended because those who need them are not utilizing them. Data from the 2005-2008 National Surveys on Drug Use and Health revealed that a vast percentage of young opioid-dependent patients with pain (83%) perceived no need for intervention targeting their opioid use, reported significant worry about their ability to manage chronic pain without opioids, and were concerned about stigma associated with these interventions (Wu et al., 2011). Indeed, these same concerns (particularly stigma) have been identified in military and Veteran populations (Sirratt et al., 2012), and the rates of untreated substance abuse among military Veterans are now twice as high as rates of untreated serious psychological distress Golub et al., 2013). There is now a significant need for research testing non-pharmacological pain management programs that can curtail opioid use in polymorbid Veterans. Interdisciplinary pain programs offering alternative pain management strategies may offer a dual benefit of improved pain coping and decreased opioid use. In fact, our research group generated preliminary evidence showing a significant reduction in opioid prescriptions after interdisciplinary pain treatment in a non-combat injured military sample.

The Department of Veterans Affairs has recently implemented a broad initiative to address opioid dependence, abuse, and misuse in Veterans. This Opioid Safety Initiative (OSI; described in detail in Section 5.3.4) was designed to better manage the opioid prescription process and develop alternative pain management options for veterans with chronic pain who, especially those who are "chronic opioid users." Indeed, ample data exists describing the significant risks

of opioid use in the VA and the high rates of persistent opioid use or misuse especially among veterans with pain and psychiatric comorbidities (Seal et al., 2012).

The few publications describing the effectiveness of the OSI show a significant drop in the rate of opioid prescription in the VA system, especially for veterans on high doses of opioid medications (Westanmo et al., 2015). A PCORI Topic Brief published in June 2015 provides a comprehensive review of the data on safety and efficacy of opioid medications, and the available data largely show that opioid medications are "weakly" effective in the long-term management of chronic pain and there is very little data describing the best way to discontinue opioid medications, and no good research describing the long-term consequences for pain management and opioid recidivism for those who are discontinued (which mirrors Congressional Testimony by VA Official Dr. Robert Petzel in 2014 describing a large reduction in opioid prescriptions throughout the VA attributable to OSI. The South Texas Veterans Health Care System, where this study will take place, was recently identified as a top ten performer for OSI outcomes, so STVHCS veterans are increasingly likely to become former opioid users.

Although there is little VA data describing the outcome of opioid prescription tapering or discontinuation in veterans, there is some helpful data offering insight into what could occur. A small-scale study of an Opioid Renewal Clinic in the Philadelphia VA found a recidivism rate of over 40% for veterans who discontinued opioids (with higher rates for those not engaged in an intervention program for high risk opioid abusers; Becker et al., 2009). An older study of Vietnam veterans also found a 40% rate of future opioid use after military discharge among veterans who were "addicted" to opioid medication during active duty service (O'Brien et al., 1980). A rat-model study of opiate withdrawal after chronic opioid treatment found an increased rate of cocaine-seeking behaviors (He & Grasing, 2004).

2.2 Study Rationale

Interdisciplinary pain management is now a high priority for the DoD and VHA. The United States Army assembled a Pain Management Task Force in 2009 with the mission of outlining gaps in chronic pain management resources throughout the DoD and VHA medical systems. It completed site visits with pain management specialists at VHA and DoD facilities throughout the United States (including with the PI of this proposed research) to identify potential best practices in military chronic pain management. In its 2010 Final Report, the Task Force emphasized a need for pain management resources that go beyond medication and other one-dimensional interventions, specifically emphasizing the need for Complementary and Alternative Medicine (CAM) approaches. They noted that most DoD and VHA providers feel ill-prepared to manage chronic pain and are unaware of resources for pain management beyond medications and physical therapy. Specifically, the report outlined the need for standardized interdisciplinary programs offering improved pain management with the benefit of decreased risk of opioid abuse. These interdisciplinary programs are likely to result in vast improvements in function, healthcare utilization, and quality of life for military Veterans with chronic polymorbid pain (McGeary et al., 2006; McGeary et al., 2010), and would severely decrease adverse risk associated with long-term opioid use/abuse in this population saving the federal government billions of dollars in healthcare costs. The study PI recently published a paper in the *American Psychologist* (March 2014) describing the significant benefit of integrated/interdisciplinary pain management programs over independent pain management interventions (Gatchel, McGeary, McGeary & Lippe, 2014). In this paper, the authors note that psychological interventions for chronic pain are most useful as an embedded component of a larger, multi-component program including

disciplines oriented toward improving physical functioning. This is particularly important for military and Veteran populations for whom physical functioning is a vital part of their jobs and identities. When developed well and integrated appropriately, psychological interventions can significantly enhance and improve outcomes from other pain management interventions (e.g., PT). Previous studies of interdisciplinary pain programs (including the original FORT study) have consistently shown that these interdisciplinary programs outperform individual treatment like PT.

Some steps have already been taken to develop interdisciplinary care for polymorbid Veterans. In 2004, the U.S. Congress passed Public Law 108-422, Section 302 and Public Law 108-447, both of which require the development of integrated VHA specifically addressing deployment-related polymorbidity (Cifu et al., 2009; Eapen et al., 2013). One consequence of this legislation was the establishment of the VHA Polytrauma System of Care (PSC), which built and staffed 5 Polytrauma Rehabilitation Centers (PRCs) across the United States to serve as referral hubs for OEF/OIF/OND Veterans with complex polymorbid conditions. These PRCs currently offer the highest level of intervention available to polymorbid Veterans. Despite these advances, there are still significant gaps in the management of complex chronic polymorbid pain that severely challenge caregivers and Veterans alike. PRCs are equipped with multiple disciplines necessary to adequately address the complexity of polymorbid chronic pain, but these services are not adequately integrated for polymorbid pain management [9]. This integration is difficult, and there are very few interdisciplinary pain management programs that have been proven effective in military-relevant pain populations. Our research team was one of the first to test a truly integrated model of pain management in a military population which we called the Functional Orthopedic Treatment program (FORT). Recently, the Affordable Care Act has laid out plans and instructions for the proliferation and promulgation of interdisciplinary pain management services (see Gatchel, McGeary, McGeary & Lippe, 2014).

The FORT program was originally tested in a non-polymorbid active duty military chronic pain sample. The original trial showed that our model of integrated care can effectively improve physical and psychosocial disability among military service members with pain. It has yet to be tested in a polymorbid pain population, but we believe that the CAM-based composition of FORT makes it an excellent substrate for polymorbid pain management. We have expanded on the original FORT trial through several subsequent trials specifically focusing on pain processes in polymorbid military members and Veterans. Data from these subsequent trials have allowed us to tailor the FORT intervention to the specific needs of a polymorbid OEF/OIF/OND Veteran chronic pain population. We have labeled this amended version of the manualized program "FORT-A" (A = Amended), and believe that this new program offers the best available opportunity for polymorbid pain management. The proposed study will recruit 130 OEF/OIF/OND Veterans with polymorbid chronic musculoskeletal pain who are currently using chronic opioid therapy for pain (taking opioid medications daily for 20 out of 30 days a month for three or more months). In 2015, the VA Opioid Safety Initiative (OSI) began to programmatically work toward improving the safety of opioid medication prescription for San Antonio Veterans with chronic pain. As noted above, very little is known about the potential outcomes of this initiative, but the scant available data suggest a rate of opioid recidivism of 30-40% among prior persistent opioid users who get no specialty intervention. To align with this initiative, this study altered the opioid inclusion criterion to include Veterans who were removed from opioid medications during the OSI. These Veterans will be randomly assigned to either the 3-week interdisciplinary FORT-A chronic pain management program (described below) or to

treatment in the South Texas Veterans Health Care System's (STVHCS) PRC in San Antonio, TX, which represents the best available care for Veterans with deployment-related polymorbid pain. Primary endpoints for this research include pain management (represented in Aim 1) and opioid use (represented in Aim 2) at pre-treatment, post-treatment, 6-month follow-up and 12-month follow-up.

3. STUDY DESIGN

To address the primary and secondary hypotheses, this research study was designed as a randomized clinical trial comparing the manualized FORT-A treatment to treatment as usual for polytraumatic chronic musculoskeletal pain in the STVHCS Polytrauma Rehabilitation Center. Eligible OEF/OIF/OND Veterans will be randomized to either arm in 1:1 random permuted block randomization with no stratification. Because the FORT-A is a group intervention, it is vital that we randomize into meaningful blocks of at least three Veterans and no more than seven. Three is chosen as the lower block boundary because the PI had success in the original FORT trial with FORT groups of three active duty service members. Seven Veterans will be the upper boundary because FORT groups of more than seven military members were difficult to manage. In block randomization with static boundaries, study staff overseeing randomization will lose blinding if they are aware of how many participants have already been randomized into each block. For example, if block boundaries are always 5 participants and the treatment as usual condition has 5 participants while the active treatment has 4, then the staff randomizing the 10^{th} participant will know with certainty that this participant will be in the active treatment group. To protect blinding, we have chosen to implement a variable boundary randomization for which the study staff randomizing patients will be blind to the boundaries and the resulting condition of the participant (see Sanghaei, 2011). The PI, Independent Evaluators, and Biostatistician will be blind to the condition of all participants until data lock. A research assistant overseeing randomization will also be blinded by randomizing unique patient identifiers into variable permuted blocks (through the STRONG STAR Data Core) by unique study identifier (e.g., first participant identified as #0001). All assessments given by Independent Evaluators will be labeled with just the unique identifier. Only the study coordinator (and co-coordinator) will be able to link unique identifiers to individual participants.

This research study covers two objectives/aims encompassing four formal hypotheses and one exploratory objective. The primary objective of this research is to assess the efficacy of the FORT-A program for improved pain management in a sample of 130 polymorbid OEF/OIF/OND PRC-eligible Veterans with chronic musculoskeletal pain compared to standard care in the STVHCS Polytrauma Rehabilitation Center. A second objective will assess the efficacy of FORT-A in decreasing the rate of opioid use among eligible Veterans with recent and ongoing persistent opioid use. An exploratory objective will explore how certain variables (helplessness and perceived burdensomeness) contribute to change trajectory over time.

Table 1. Pearson correlation between 4 disability measures and other notable FORT outcomes.

Pearson's r	FTW	WTE	ODI	MVAS
Depression	-.174	-.278	.690	.424
Fear Avoidance	-.106	-.184	.622	.530
Pain Rating	-.099	-.219	.856	.816

The primary outcome of this research (addressing AIM 1) is disability rating (consistent with functional restoration theory emphasizing functional ability over changes in pain intensity, frequency, duration, or quality). This study was designed to assess disability objectively (functional capacity evaluation; FCE) and subjectively (self-reported disability scale). Data from the original FORT trial revealed that self-reported disability had a stronger relationship with psychosocial and socioeconomic pain management outcomes than objective functional capacity (see Table 1 for an example). Furthermore, self-reported disability is likely to be more sensitive to improvements in psychological pain management skills (which is central to this research). For this research study, the Oswestry Disability Index (ODI, Version 2) will be used to measure self-reported disability. ODI was chosen for this purpose because the significant body of research supporting its use and its performance beyond other measures of self-reported disability in the FORT trial.

The secondary outcome (addressing AIM2) for this research is rate of opioid medication recidivism. In consultation with study co-I and opioid dependence/misuse expert, Dr. Jennifer Potter, we decided to adopt a conservative definition of recidivism of use of any opioid for three days in any 30-day period. This definition was chosen (instead of a non-abstinent definition as described in McCabe et al., 2013) because this medical population may include veterans given short-term opioid therapy for a new injury or surgery and we did not want to count that as relapse or recidivism to opioid use. As was the case for disability, opioid use will be assessed through objective (MEMS caps) and subjective (timeline followback interview; TLFB) methods. Because some participants may shift patterns of other pain medication use as a result of discontinuing opioids, we will also complete TLFB for other pain medications and ask participants to use MEMS for their "most helpful" pain medication (if they are not taking an opioid med). All opioid medication use will be measured with MEMS and TLFB. We will also assess pain medication using the Medication Quantification Scale – III (MQS). The MQS was developed through the American Pain Society as a standardized method of quantifying pain medication use along dimensions of drug class, drug dose, and drug detriment (Harden et al., 2005). Both TLFB and MQS data will be gathered monthly (at all assessment intervals in person) and during monthly reminder phone calls. Previous studies have shown that Timeline Followback interviews demonstrate the best reliability and validity for long-term medication use (Kunoe et al., 2009), so TLFB was chosen as the focal secondary outcome measure for this research.

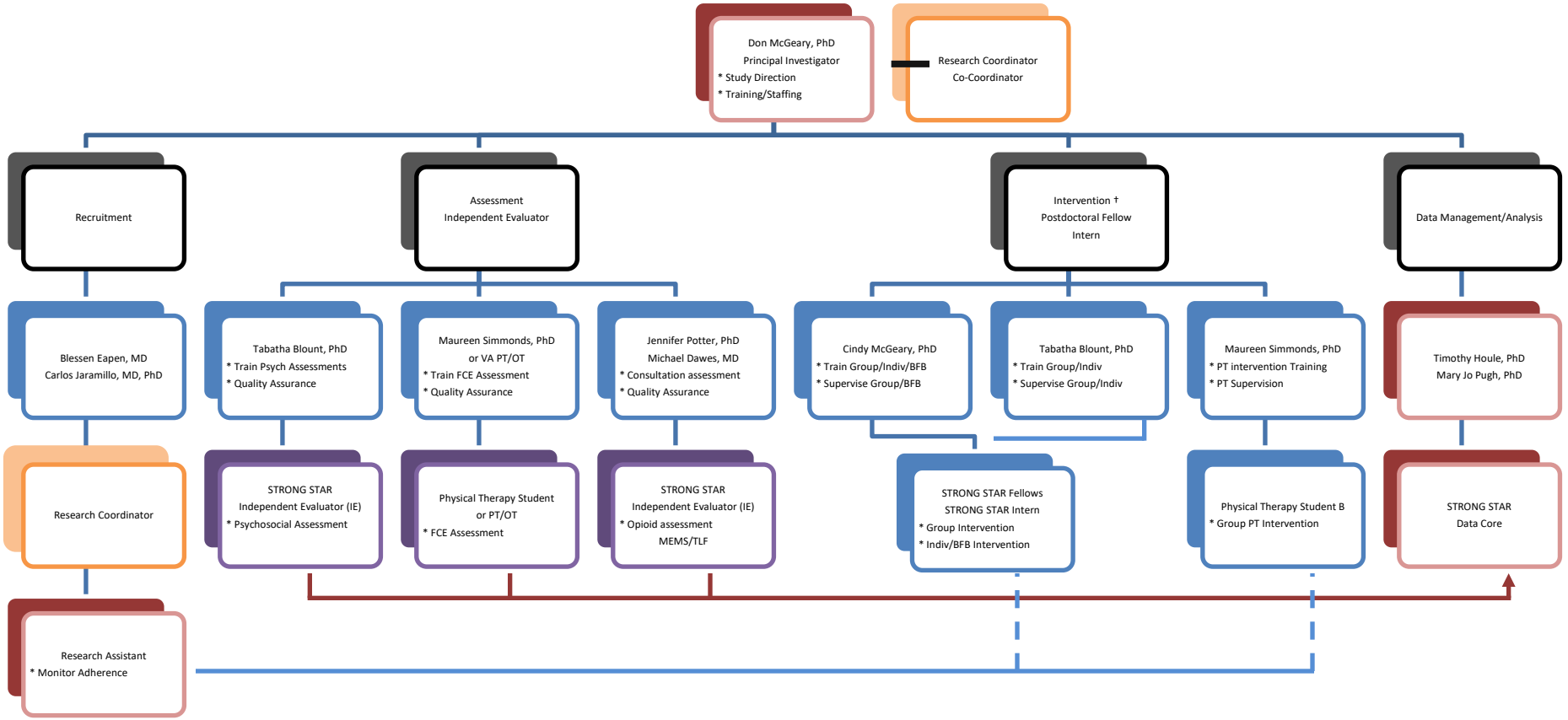
Based on our previous FORT trial, for which treatment effects in the FORT study arm were maintained at one-year follow-up, it is reasonable to assume that treatment benefits will be maintained after post-treatment and that all post-baseline measures can be averaged for a main effect of treatment. To detect a medium effect with power = 0.80 (based on Cohen's standardized mean difference d=0.50) at $\alpha = 0$ .05, we would require n=50 in each study arm for a total sample size of N=100 for data analysis. Based on our prior FORT research trial and our ongoing VA trials through STRONG STAR, we anticipate less than 30% attrition with a target recruitment goal of n=65 in each arm to account for dropouts. Thus the recruitment target for this research is 130 OEF/OIF/OND Veterans with military service-related new onset or exacerbated chronic musculoskeletal pain and persistent opioid use. Both the FORT-A and PRC treatments will be provided on an outpatient basis through the STVHCS PRC (where the PI has several hundred square feet of research space under a VA WOC appointment; see 5.1 and 5.2 in

this document for a more detailed description of the treatment arms). The overall trial will last 5 years (2014-2019). The IRB protocol for this research was approved on July 10, 2014 (see study binder for most current IRB documents and any amendments submitted and approved to the UTHSCSA/VA IRB). Individual participants will be actively enrolled for one year during which time they will:

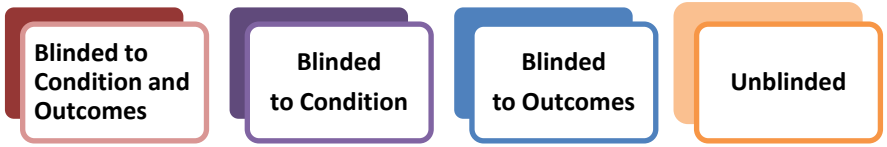
- Complete pre-treatment assessments
- Undergo a three-week treatment phase
- Complete post-treatment assessment
- Complete 6-month post-treatment follow-up assessments
- Complete 12-month post-treatment follow-up assessments

The following diagram (Figure 2) outlines the administration for this research and the blinding status of individual study personnel/roles:

Figure 2. Study organizational hierarchy



Key:



4. SELECTION AND ENROLLMENT OF PARTICIPANTS

Participants for this research will include (N=130) U.S. military Veterans treated through the South Texas Veterans Health Care System (STVHCS) for chronic musculoskeletal pain associated with deployment to OEF/OIF/OND (see *Inclusion/Exclusion Criteria* below). Eligible Veterans can have multiple pain concerns, but their primary pain concern must be musculoskeletal pain. All eligible Veterans must be a prior persistent opioid user who was removed from their opioid medication by their VA provider. Participants will be recruited through the STVHCS Polytrauma Clinic, the STVHCS Pain Management Service, and the STVHCS Primary Care Service. They will be eligible for care in the PRC. Our PRC partners estimate that they enroll approximately 30 new patients at the PRC per month, roughly 80% of whom would meet criteria for this research. We will recruit through direct provider referrals and advertisements posted in VHA clinics; both of these strategies have been quite successful in both the original FORT trial and our ongoing STRONG STAR research efforts. Our PRC collaborators (Dr. Jaramillo and Dr. Eapen) will ask their staff to introduce the study to new PRC patients and will be available to answer questions. This research has been adopted as a STRONG STAR initiative, and will have access to STRONG STAR resources and procedures for recruitment. This will be of significant benefit because STRONG STAR studies routinely achieve their recruitment targets through local advertising, media exposure for the consortium, and solid working alliances with VHA and DoD service providers. Based on our experience with numerous STRONG STAR trials and the original FORT trial, we expect <30% attrition and have factored this into our recruitment target. Participants will be reimbursed for time and travel.

4.1 Inclusion Criteria

Study participants must meet all of the inclusion criteria below to participate in this study as follows*:*

1) Demographics for inclusion in this research include both genders, all racial/ethnic groups, and ages 18-72.

2) Present with chronic musculoskeletal pain (CMP) as a primary pain complaint

3) CMP is accompanied by at least moderate disability based on a score of 20% or more on the Oswestry Disability Index;

4) Consistent with NIH Task Force recommendations, "chronic" CMP has been a problem for the Veteran for at least half the days in the last 3 months and was acquired or exacerbated as part of active duty U.S. military service in the Gulf War, Operations Iraqi Freedom (OIF), Enduring Freedom (OEF), or New Dawn (OND) war eras.

5) CMP presents in the context of comorbid psychiatric symptoms of posttraumatic stress disorder (PTSD; based on a score of 25 or more on the PTSD Checklist-Version 5) and/or depression (based on a score of 10 or more on the PHQ-9).

6) Demonstrate prior "chronic" opioid use (defined as using opioid medication for 20 out of every 30 days over three or more months) and discharged off of persistent opioid medications on their own or by a provider for at least one week prior to the pain management program period (Weeks 1-3).

7) Speak and read/understand English well enough to fully participate in the intervention and to reliably complete assessment measures.

8) The Veteran will be eligible to be a PRC patient (i.e., have multiple trauma related physical and psychological injuries; VA, 2013) and be eligible for Physical Therapy referral through the PRC (though the referral for the same service could also come from another VHA provider). All participants will be offered Physical Therapy services before enrollment and will be enrolled after completing or denying Physical Therapy.

4.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria below at baseline will be excluded from study participation:

1) Actively engaged in an intervention or program specifically targeting opioid use (including those using naloxone).

2) Present with active psychosis or suicidal ideation with intent. These symptoms must be stabilized (i.e., maintained at or below moderate intensity for 6 weeks with no acute episodes requiring higher levels of intervention) through a VHA Psychology or Psychiatry referral and confirmed by the mental health provider before the Veteran is eligible to participate.

3) CMP is not related to or exacerbated by military service during the OEF/OIF/OND combat eras.

4) Present with significantly diminished decision-making capacity (e.g., severe cognitive dysfunction related to severe TBI).

5) Pregnant women

6) Inability or unwillingness of individual or legal guardian/representative to give written informed consent.

4.3 Study Enrollment Procedures

- Potential participants may be directly referred to the study by their VA provider or may directly contact the study coordinator on their own in response to flyers/pamphlets distributed at VA clinics

- Consistent with current STRONG STAR practices, we will maintain an Enrollment Log describing the timeline of screening and consent as well as the disposition and reason for enrollment/disqualification (see **Appendix A3**).
- Consent for participation in this research will take place in the South Texas Veterans Health Care System (STVHCS) PRC or on the STVHCS Bartter Research Unit (BRU). Potential participants who are referred by a provider or who self-refer in response to a flyer will call the study coordinator and arrange a time to meet and discuss the study. Those who sign a **Consent to Contact** form after meeting with their physician at the STVHCS (**Appendix A1**), will receive a phone call from the study Coordinator. Participants will be asked to meet individually in a private room at the PRC/BRU with the Coordinator where they will be told about the study and will have an opportunity to ask any questions they may have of the Coordinator. Potential participants will be given a copy of the study informed consent document (ICD, **Appendix A2**) and will be allowed to take it home with them if they wish to take time to read it. Upon reading the document, the potential participants will have an opportunity to ask questions about the study and may meet with a study investigator to address their questions. Consistent with STRONG STAR procedures, the Coordinator will have a checklist of questions about the ICD that they will ask the potential participants to ensure that they understand. Once understanding is confirmed, the participants will sign the ICD and be enrolled into the study and recorded on the NCCIH Enrollment Form (**Appendix A3**). A unique identifier will be assigned to the participant using a code developed in accordance with the STRONG STAR Unique Identifier SOP (**Appendix A4**).
- Participants will be randomly assigned into one of the two study arms (FORT-A, Treatment as Usual) on a 1:1 ratio. Participants will be randomized using variable sized blocks of an even number to maintain a balance within blocks. One weakness of block randomization is that blinded study staff who are aware of established block sizes will be able to predict, with increasing certainty, how a participant will be randomized as blocks fill. This does pose a threat to blinding and creates an opportunity for non-random assignment (e.g., cherry picking a participant who may be a particularly good responder to be "randomized" into the experimental condition). To maintain a blinded assignment schedule, we have chosen to work with the STRONG STAR Biostatistics and Data Core to execute the randomization schedule, hold the blinded assignments, and administer them to the study Coordinator sequentially during enrollment (i.e., the Coordinator and study team will always remain blinded to the next assignment)

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

FORT-A

Although pain programs like FORT-A have been explored in civilian pain populations (McGeary et al., 2006; Mayer et al., 2004; Proctor et al., 2004), military and Veteran research has been limited. FORT-A is a particularly good fit for military and Veteran populations because the focus of treatment is on return to function, not on palliative pain relief. This works well for military and Veteran pain sufferers who are used to "biting back" pain and pressing on with their mission. When we first developed the FORT program, we included a number of newly emerging complementary and alternative medicine interventions that were starting to show promise in pain research (mindfulness, biofeedback, relaxation strategies, motivational interviewing, acceptance and commitment therapy, guided exercise and activity – including mind-body exercises like yoga). Outcomes from our DoD-funded study of FORT revealed significant improvements in pain management (Gatchel et al., 2009). CAM interventions have been strongly emphasized in the FORT-A manual (see Appendix) based on participant feedback from the original FORT trial and from research subsequent to the FORT study demonstrating very little beneficial effect of cognitive-behavioral therapy (CBT) for military pain management. We have kept some CBT elements to address cognitive variables that are implicated in psychosocial adjustment to chronic polytrauma pain based on the PI's current DoD-funded trials (Kanzler et al., 2012). FORT was augmented to include a stronger emphasis on CAM interventions that are most likely to promote pain management and opioid sparing among polymorbid OEF/OIF/OND Veterans, and the augmented program has been labeled "FORT-A." FORT-A is provided on an outpatient basis and includes 12 daily group pain management and physical therapy sessions spanning three weeks. Group interventions are supplemented by individual psychotherapy, biofeedback, and case staffings. CBT sessions were decreased in favor of CAM components. FORT-A participants will receive 270 minutes (4½ hours) of intervention a day for 12 days over 3 weeks. All FORT-A interventions will occur at the STVHCS PRC in dedicated research space. FORT-A includes:
*** 12-session outpatient group intervention**. The FORT-A group occurs 4 times a week for 3 weeks (12 total sessions) for 90 minutes each. Topics include:

- *goal-setting* (2 sessions)
- *relaxation strategies* (4 sessions)
- *mindfulness for pain management* (2 sessions)
- *CBT for pain management* (2 sessions)
- *communication and social support* (1 session)
- *motivational interviewing and managing stages of pain* (1 session).

> Potential Adverse Effects (**risk**): discussing pain management may make pain more noticeable, resulting in perception of increased pain intensity (**NOT SERIOUS**)

*** 2 weekly sessions of outpatient individual psychotherapy** for PTSD, depression and pain management (6 total sessions) for 75 minutes each (15 minutes to check on pain management topics covered in group; 60 minutes for Prolonged Exposure for PTSD symptoms based on the manualized approach used in our current STRONG STAR study). Individual sessions (depression, PTSD) may be conducted by other clinic providers if subject is already engaged in treatment prior to enrollment. If sessions are conducted by another provider, the quality of care will be standard clinical care which is appropriate for this protocol; however, the duration of care may be variable so we will be tracking number of sessions attended. For

those subjects receiving Individual sessions from another clinic provider, the 15 minute pain management session will be included with their biofeedback session. Most participants reported accomplishing little in these sessions beyond what was already done in the group. In a *polymorbid* Veteran sample, it is vital that trauma symptoms (PTSD and depression) are addressed along with pain (Lew et al., 2009). PTSD will be addressed using a modified Prolonged Exposure (PE) protocol and depression will be addressed through Behavioral Activation.

> Potential Adverse Effects (**risk**): PTSD interventions like PE may result in an increase in PTSD symptoms severity (as the Veteran overcomes avoidance of symptoms) during the first week of treatment (**NOT SERIOUS**)

*** 12-session physical therapy (PT)**. PT sessions occur 4 times a week for 3 weeks (12 total sessions) for 90 minutes each. As in the original FORT trial, PT will occur immediately before the group intervention. Each patient will be given an illustrated PT manual supplemented with a CD that provides information on pain and activity and includes an individualized workbook for setting, prioritizing, and completing activity related goals. Each 90 minute session will include a presentation/discussion on a key topic and group exercise targeting strength, flexibility, and aerobic speed interval training to address psychomotor slowing.

> Potential Adverse Effects (**risk**): PT may result in muscle soreness (**NOT SERIOUS**) or musculoskeletal injury/worsening of injury (**SERIOUS**)

*** 2 weekly sessions of biofeedback** (6 total sessions) for 30 minutes each. Biofeedback is given to all participants as an adjunct to relaxation training, hypnosis/meditation, and postural changes.

> Potential Adverse Effects (**risk**): None

*** 1 weekly interdisciplinary case staffing** (4 total staffings, one at pre-treatment and one at the end of each program week) for 60-90 minutes each. The FORT-A clinical psychologist and physical therapist meet with the case manager/coordinator, and a Physical Medicine and Rehabilitation physician to discuss each patient's treatment plan, progress with treatment goals, medication, and barriers to care.

> Potential Adverse Effects (**risk**): None

"Typical" FORT-A Day	
Time	**Activity**
0800-0830	FORT-A Pain Management Group
0830-0900	
0900-0930	
0930-1000	Group-Based Exercise
1000-1030	
1030-1100	
1100-1130	Individual Psychotherapy

1130-1200	-OR- Biofeedback

Polytrauma Rehabilitation Center (PRC)

PRCs offer the highest level of care for polytrauma Veterans. They serve as a "hub" for clinical referrals, training, and education in polytrauma care (Eapen et al., 2013). Each PRC includes Physiatry, Rehabilitation Nursing, Physical Therapy, Psychology, Family Therapy, Occupational Therapy, and other specialties (VA, 2013). Treatment goals for PRC Veterans are decidedly functional, emphasizing return to work, community integration, improved psychosocial functioning, and enhanced coping skills (Eapen et al., 2013; Braverman et al., 1999; McNamee et al., 2009). Chronic pain management is a high priority for the PRC, and pain represents *the most commonly reported* clinical concern among PRC Veterans (Sayer et al., 2009). The logistic organization of the PRCs offers an excellent opportunity for clinical service and stakeholder integration (Strasser et al., 2008). The proposed research is vital for pain management in the PRC. Although PRCs succeed in locating multiple treatment resources in the same clinic, they have yet to produce consistent evidence of truly successful, integrated chronic pain management (Strasser et al., 2008). Our research group has hypothesized that PRC pain management primarily suffers due to a lack of guidance on how to most effectively integrate polymorbid pain treatment resources. Indeed, PRC clinicians have openly indicated the need for more guidance on service integration in PRCs to help them more effectively manage the complexity of deployment-related polymorbidities (Clark et al., 2009; Friedemann-Sanchez et al., 2008). *An intensive program like FORT-A offers surprisingly little treatment burden to PRC staff and patients compared to the current standard of care.* Veterans treated in the PRC are often required to attend multiple appointments throughout the week, requiring substantial time away from work. Current protocol for chronic pain management through the San Antonio PRC (our partner for this research) is for each PRC Veteran to complete 12 sessions of Physical Therapy over 3 to 4 weeks, with supplemental appointments for medication, pain injections (e.g., epidural steroid injections), and assessment as prescribed by the Veteran's treatment team. Evaluation clinics at the PRC typically last over 4 hours and Veterans typically attend 12 or more sessions of PT over 3-4 weeks. Few other services are provided for pain and our PRC collaborators note that PRC pain outcomes resemble the moderate functional gains typically demonstrated by Veterans undergoing standard physical therapy for chronic pain management (Garcia et al., 2013; Brooks et al., 2012; Groessl et al., 2012). For this research, Veterans randomized to the PRC will receive 3 weeks of PRC services as recommended by their interdisciplinary team (which could include PT, occupational therapy, counseling, or medical management; Eapen et al., 2013).

All study participants will be offered PRC Physical Therapy before randomization. PRC physical therapy (PT) varies in frequency and duration based on pain presentation, but can occur daily for up to three weeks. PT sessions are individualized, so length of the session will vary from patient to patient.

> Potential Adverse Effects (**risk**): PT may result in muscle soreness (**NOT SERIOUS**) or musculoskeletal injury/worsening of injury (**SERIOUS**)

Not all PRC patients are recommended for, or taken advantage of, the full slate of PRC services (e.g., Family Therapy, Psychology, Occupational Therapy), but all are seen and followed by a Physical Medicine & Rehabilitation Physician and/or Nurse Case Manager at biweekly up to monthly follow-up intervals.

Potential Adverse Effects (**risk)**: Variable (depending on medical or psychological interventions (**INDETERMINATE**)

The PRC manages chronic pain in accordance with the VA/DoD Clinical Practice Guidelines (CPG; which can be found at http://www.healthquality.va.gov/). Interventions for pain management in the PRC may include (but are not limited to) the following based on the CPG (which should be consistent across Polytrauma System of Care sites):

PRC Treatment Component	Adherence Management/Tracking
Diagnostics	
(Imaging, ESR)	None
Self Care	
Advice to Remain Active	Consult Chart Interview with Participant
Education	
Books, Handouts	Consult Chart Interview with Participant
Medication	
Acetaminophen NSAIDs Antidepressants (TCA) Benzodiazepines Opioids	Consult Chart Opioids and Other Pain Meds: MEMS, Timeline Followback, MQS Interview with Participant
Physical Therapy	
PT through PRC/PT Service	Consult Chart Functional Capacity Evaluation Interview with Participant
Other Non-Pharmacological Therapy	
Spinal Manipulation Exercise Therapy Massage Acupuncture Yoga CBT Relaxation Intensive Interdisciplinary Rehabilitation	Consult Chart Interview with Participant

5.1.1 Physical Therapy in the PRC Treatment as Usual

All study participants will receive a recommendation for Physical Therapy (PT) at pre-screening (before enrollment) to ensure that prior participation in "standard" PRC PT does not confound study results (and most PRC patients with pain receive a recommendation for PT as part of standard care). This is necessary to ensure that there are not differences in enrolled participants based on their prior exposure (or opportunities for exposure) to PT before participating in the study. Those who have previously completed PT through the STVHCS or have declined participation will be enrolled and randomized for this research (if they otherwise qualify). Participants in the PRC Treatment as Usual study arm will *not* receive another recommendation for PT through the PRC because a second recommendation is not standard care in the PRC. They are not prohibited from attending PT again, but a second recommendation for PT in the Treatment as Usual arm will not be provided as part of this research.

5.2 Handling of Study Interventions

The active intervention for this study is based on an integrated, interdisciplinary approach involving group psychotherapy, individual psychotherapy, physical therapy, biofeedback, and weekly interdisciplinary team meetings. Each phase of the active intervention is described below including methods for ensuring intervention accountability and masking. A formal manual is available to guide the group intervention (see **Appendix B**) and the Individual Psychotherapy (which uses a 6-session manualized intervention for PTSD based on Edna Foa's Prolonged Exposure protocol with some elements of behavioral activation to address depressive symptoms). A Manual of Procedures (MOP) is being developed to guide biofeedback, Physical Therapy, and Interdisciplinary Staff Meetings (to be **Appendix C**). Only basic details are provided for use of intervention in this section. More details for interventions, interventionist training, and assessment of adherence to treatment are found elsewhere in this manual as follows:

* Section 5.1 of this protocol provides more detailed information about the content and structure of the intervention components.

* Section 5.4 of this protocol provides more detailed information about adherence assessments and certification of study interventionists)

Group Psychotherapy (see Group Manual, Appendix B)

As described in section 5.1 of this protocol, the group psychotherapy component of the FORT-A intervention is a twelve-session program occurring in the morning, four days a week for three consecutive weeks. Currently, the group is scheduled to occur from 0900-1030 at the PRC. The group intervention is guided by a comprehensive manual to which the group interventionist (a STRONG STAR Intern or Fellow) must adhere. All STRONG STAR Interns and Postdoctoral Fellows are credentialed as Without Compensation (WOC) providers in the STVHCS and are supervised by a licensed Psychologist (Dr. Cindy McGeary, Dr. Tabatha Blount) and administratively overseen by a licensed VA Psychologist (e.g., Dr. Emma Mata-Galan, though this may change with Dr. Mata-Galan's promotion to Psychology Chair). All group

sessions are audiotaped and 10-15% of all audiotaped group sessions will be selected for review by a trained independent evaluator who will use a structured checklist to ensure that all significant treatment elements are included in the intervention. Interns and Fellows will be formally trained in the manualized group intervention by Dr. Don McGeary (who developed the intervention and created the manual) and will co-facilitate a group intervention with Dr. D or C. McGeary at the PRC to practice the intervention in vivo. All groups will be documented in CPRS using a standard note template. The PI (and other blinded study personnel) will not review any of this documentation. CPRS notes for group and individual treatment components will be overseen and cosigned by Dr. C. McGeary and Dr. Tabatha Blount.

Blinding: To maintain blinding, the PI will not be involved in any group interventions. Independent Evaluators (IEs) assessing group intervention facilitator adherence will be different people than the IEs responsible for assessments (because the assessing IEs may recognize voices on the tapes from their assessment experiences and may become unblinded as a result).

Providers and Qualifications: FORT-A Group Intervention will be delivered by STRONG STAR Clinical Psychology Interns and Postdoctoral Fellows (a total of 4 possible providers who will rotate through different groups). The structure of the manual and skills contained therein were developed for use by individuals with previous exposure to basic CBT and mindfulness skills commonly taught as part of the UTHSCSA Clinical Psychology Internship curriculum (and most other APA-Accredited Psychology Internships). Group intervention providers will be trained by Dr. Don McGeary and will observe one iteration of the FORT-A Group with Dr. Don McGeary, Dr. Cindy McGeary, or Dr. Tabatha Blount (all of whom have been trained on the components of the manual and who had a hand in developing the manualized intervention). To run the group without Dr. C. McGeary or Dr. Blount present, the Intern or Fellow must be certified using the procedures outlined in Section 5.4 of this document.

Individual Psychotherapy

A previous study completed by the PI in collaboration with Dr. Robert Gatchel and Dr. Alan Peterson through the STRONG STAR PTSD Research Consortium revealed that a brief, Prolonged Exposure (PE) protocol can have a meaningful effect on PTSD symptoms, though PE in isolation did not appear to impact chronic pain symptoms. The PI has previously described how PTSD symptoms can interact and affect pain experience, so PTSD (and concomitant depression) must be addressed as part of this interdisciplinary intervention to ensure that PTSD does not act as a barrier to pain management intervention. Because of its success in the previous STRONG STAR trial, this study will use the brief PE manualized intervention used in the previous trial (5 sessions) with an additional session of behavioral activation (serving as the first session) to address depression symptoms. All STRONG STAR Interns and Fellows receive world class training in PE and their supervision will be overseen by Dr. Cindy McGeary, master trained in PE by Dr. Alan Peterson and Dr. Edna Foa, and Dr. Tabatha Blount (also trained in PE through STRONG STAR). All individual sessions will be documented in CPRS.

Blinding: Neither Dr. Blount nor Dr. C. McGeary are involved in assessment of participants and will be asked not to discuss specific (i.e., identifiable) details of the interventions with the PI or other study personnel blinded to treatment condition (see Figure 2).

Providers and Qualifications: Individual treatment providers must he certified in Prolonged Exposure for PTSD (PE) or supervised by a certified PE provider. Because of this, only STRONG STAR Interns and Postdoctoral Fellows or licensed Psychologists (Dr. C. McGeary, Dr. Blount) can provide individual intervention for this research (a total of 5 different providers). Individual providers must have completed a two-day training in PE (mandatory for STRONG STAR Faculty, Fellows and Interns) and must be certified in PE as described in Section 5.4 of this document. PE is commonly practiced and taught throughout the VA system, drastically improving the generalizability of this component of the treatment manual.

Biofeedback (Manual Under Development)

Biofeedback is an adjunct to behavioral intervention that can have significant benefit for a number of behavioral and physical health concerns including chronic pain management. Dr. Don McGeary ran the biofeedback lab for Wilford Hall Medical Center (Lackland Air Force Base) for over 5 years and has certified close to 100 military Psychologists in biofeedback (BFB) use. He will train all STRONG STAR Fellow interventionists for this study and will supervise biofeedback methodology (i.e., address questions about instrumentation, interpretation, and clinical application of BFB data (which must be deidentified before being shown to the PI). Because BFB will be used differently with each participant, there is no way to manualize this part of the intervention. There will be a section of the MOP (under development at the time of this protocol draft) that will cover biofeedback instrumentation procedures and clinical documentation of encounters.

Blinding: Identifiable clinical issues will need to be discussed with Dr. Blount and Dr. C. McGeary and will not be shared with the PI.

Providers and Qualifications: Biofeedback providers must have minimal competency in basic principles of health behavior change and mindfulness. Both STRONG STAR Interns and Postdoctoral Fellows may provide biofeedback intervention (for a total of 4 different providers) and will be certified in biofeedback by Dr. Don McGeary as outlined in Section 5.4 of this document).

Physical Therapy (Manual Under Development)

Group-based physical therapy will be provided by PRC Physical Therapist/Occupational Therapist and supervised by PRC Physical Therapist/Occupational Therapist or Dr. Maureen Simmonds. Dr. Simmonds is already WOC-appointed in the STVHCS (as are Dr. C. McGeary, Dr. Blount, and the PI) and will enter notes for all encounters in CPRS. UTHSCSA PT Students will also establish WOC appointments in the STVHCS and will meet with Dr. Simmonds regularly for supervision. Group PT will include a didactic session, guided exercise, and flowsheets for home-based exercise. Group PT will occur four days a week for three consecutive weeks. We found during the original FORT trial that patients

responded best to group PT on Monday, Tuesday, Thursday, and Friday with a break on Wednesday to allow for recovery. The PRC PT Service has already agreed to allow the study to use their space and equipment for study-related PT. PT providers will be encouraged to participate in FORT-A group psychotherapy sessions and STRONG STAR Interns/Fellows will be encouraged to sit in on group PT sessions (to maintain continuity in this interdisciplinary program).

Blinding: Dr. Simmonds or a PRC PT/OT will monitor adherence to recommended PT practice and will not share details of the PT with the PI or any other blinded research personnel.

Providers and Qualifications: PT will be provided by Dr. Maureen Simmonds, her Physical Therapy students with WOC appointments at the VA, or existing PRC PT/OT providers. The number of students PT interventionists over time will vary and is indeterminate but will be greater than 2. Skills required for the PT portion of the treatment will include skills for rehabilitation of chronic pain, strength and conditioning, and improved range of motion for the back and extremities.

Interdisciplinary Staff Meetings (Manual Under Development)

The entire study team (with the exception of IEs) will meet weekly to discuss progress of FORT-A participants and PRC participants. Participants will be discussed without identifiers (even using the unique identifier would unblind the PI to the condition of the participant. These meetings will be run by the research coordinator and/or co-coordinator who will be aware of patient identity in case an adverse event is noted and needs to be addressed. Issues discussed in these weekly meetings include adherence to protocol, treatment goals, problems with treatment, and changes in medication or medical status. These meetings will occur from 1200-1300 in the PRC with the VA PI's (Dr. Jaramillo, Dr. Eapen) in attendance.

Blinding: Cases will only be discussed in a deidentified fashion to avoid unblinding the PI (who must be present at these meetings to assess progress of the study, troubleshoot procedural difficulties, and offer expert clinical guidance on implementing the program. To accomplish this, the team will develop a set of identifiers for participants specific to these staff meetings that are discreet from their research unique identification number. The study coordinator/co-coordinator will maintain a link for these identifiers to ensure continuity (NOTE: THIS MAY BE TOO CONVOLUTED TO IMPLEMENT, SO WE MAY WANT TO CONSIDER SOME OTHER WAY – PERHAPS USING PARTICIPANT INITIALS, WHICH WOULD BE MEANINGLESS TO THE PI).

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

All treatments or interventions prescribed or recommended by STVHCS or other Veterans Health Administration (VHA) or Department of Defense (DoD) medical provider for a study participant is allowed. The DoD and VHA do not allow prohibition of any recommended or prescribed intervention for research purposes.

5.3.2 Required Interventions

All participants must be given an opportunity to participate in a prescribed course of as-usual Physical Therapy (PT) through the PRC (as recommended by the STVHCS Physician) before enrollment in this research. If they have already participated in Physical Therapy, choose not to participate in PT, or have already participated in PT then they may proceed with enrollment and randomization.

5.3.3 Prohibited Interventions

Research in Department of Defense and Veterans Administration covered populations may not deny or prohibit any interventions to study participants. DoD and VA IRB's will not approve research prohibiting any access to interventions for any condition, so there are no prohibited interventions for this research. Participants who receive some interventions during or after enrollment in this study may need to be excluded from per protocol evaluation but not from intent-to-treat as follows:

Enrollment in another intensive interdisciplinary pain program

Enrollment in an intensive program for substance abuse (especially those treating opioid dependence with agents like naloxone)

- If a participant was involved in one of these programs **before** study enrollment and still meets inclusion criteria, then they need **not** be excluded from per-protocol evaluation

5.3.4 Enrollment in STVHCS Opioid Safety Initiative

In October 2013, the VA launched the Opioid Safety Initiative (OSI), designed to address high dose opioid users in the VHA system. Each VISN (i.e., regional VA catchment area) is implementing the OSI differently, but the ultimate goal (as outlined in **Appendix D**) is to reduce dependence on opioid medications for the VA's highest utilizers. In VISN 17 (the catchment including the STVHCS), the OSI is being implemented through the Department of Pharmacy in a joint effort with the Department of Psychiatry and Primary Care. VISN 17 OSI efforts include surveillance of opioid use (by morphine equivalent dose; MED), categorization of STVHCS patients based on MED and misuse risk factors (e.g., diagnosis with PTSD, diagnosis with TBI, diagnosis with Depression, diagnosis with formal substance use disorder). Starting in September 2014, STVHCS medical providers will be limited in prescribing opioid medications to high utilizers in some ways that may impact persistence of use (e.g., providers may only prescribe opioid medications 30-days at a time and are not allowed to automate renewal of prescription). Study participants who are enrolled in OSI through VISN 17 may evidence a change in opioid medication response that may not be attributable to study participation (i.e., if opioid use decreases, it will be difficult to discern if changes in use are attributable to study intervention or mechanisms of the OSI). In September and October 2014, the study PI (Don McGeary) met with the VISN 17 OSI committee to discuss how this research can function in the VISN without interfering with the OSI. The OSI committee was welcoming of this study (VISN is required to have a CAM intervention program on

site and the OSI committee asked to count this research as their CAM effort), and agreed to flag study participants and delay their OSI enrollment until study participation is complete. Additionally, the OSI agreed to begin their enrollment with high risk opioid users (> 400 MED, with multiple risk factors), representing a sub-cohort (approximately n=175) of the 1,300+ Veterans in the STVHCS who will likely qualify to participate in this study. Additionally, the OSI offered to allow Dr. McGeary to continue to join the OSI committee for regular meetings (they meet twice per month) and expressed an interest in working with the PI and the IRB to explore how OSI surveillance might be used to assist in recruitment (at the time of this protocol amendment – 2.0, October 2014 – this approach to recruitment has not yet been discussed with NCCIH, has not been proposed to the IRBs of record, and has not been implemented). At present, STVHCS OSI includes the following components for enrolled participants:

- One-hour, group-based psychoeducational class on the dangers of opioid medications
- Limit of opioid prescriptions to 30 days at a time with no automatic refills (overseen in VISN 17, Chief of Pharmacy)
- Education for STVHCS on opioid prescriptions and the dangers of opioid medications and opioid misuse
- Referral for substance abuse treatment through STVHCS Psychiatry

STVHCS is currently in the process of hiring 6 new personnel for this initiative including a physician, a nurse, and a social worker (among others). As of November 2014, these positions have not been hired.

* ***Note: This section of the protocol will continue to be updated as the STVHCS OSI develops further.***

UPDATE (August 2015): In March 2015, Dr. Carolyn Clancy (Interim Under Secretary for Health, Veterans Health Administration) testified before the Committee on Veteran's Affairs in the United States Senate. She described the progress of the Opioid Safety Initiative in the VA (a transcript of her testimony can be found at: http://www.veterans.senate.gov/imo/media/doc/VA%20Clancy%20Testimony%203.26.20151.pdf). In her testimony, Dr. Clancy described a system-wide decrease in opioid medication use throughout the VA (13%) and a decrease in persistent opioid use (15%). She noted that rescheduling of hydrocodone prescription has further curtailed how opioid medications are dispensed in the VA. Finally, she reported on the significance of CAM programs for pain management as part of the OSI. Dr. Clancy's report highlights a unique opportunity for this NIH-funded study to add to this effort. The PI has been working the VA Co-PI (Dr. Eapen) to identify how the STVHCS PRC is managing OSI referrals and the PI will be working with the San Antonio OSI to establish this study as an OSI referral option (if approved by the NCCIH). This would not only vastly increase the feasibility of recruitment, but also allow for a comparison between referred and non-referred patients to add in programmatic decision making at a Federal level (regarding a program like FORT-A as a CAM referral option for OSI patients). There is no better time to do this, and addition of OSI-referred patients to our inclusion criteria would make this possible.

5.4 Adherence Assessment

Adherence for this research is addressed in the following three ways:

Adherence of interventionists and assessors to manualized assessment and treatment procedures. All interventions (FORT-A group, biofeedback, individual psychotherapy) will be provided by one of the licensed Psychologist study investigators (or supervised STRONG STAR postdoctoral fellows/interns) and a licensed Physical Therapist. Psychologists will be trained in the group intervention by the PI and then certified by Dr. Cindy McGeary using a "see one, do one" approach in which they will observe the Dr. Cindy McGeary running all 12 sessions of a clinical (non-research) group and be observed by her to obtain certification. During her observation, Dr. Cindy McGeary will use a checklist of group session content (adapted from the same checklist used in the original FORT trial) to ensure that at least 90% of required content is covered at each session. If successful (e.g., covers 90% of each session), the Psychologist will be "certified" and will be eligible to teach others. The PI will also train interventionists in biofeedback using the certification process he developed for the U.S. Air Force's biofeedback lab at Lackland Air Force Base (e.g., complete two mock biofeedback sessions with the PI before seeing FORT-A patients). Group psychotherapy and biofeedback will be supervised weekly by Dr. Cindy McGeary (the PI will be available to address technical questions about the group treatment and biofeedback, but will do this outside of supervision (in order to maintain blinding). Independent evaluators (IE's) will be trained on all psychosocial assessments by the PI and Dr. Cindy McGeary. The IE's will be trained on the timeline followback (TLFB) opioid assessment method by Dr. Blount, who will train each IE through 2 role play cases and record two clinical TLFB assessments for review. If the IE achieves a 90% success rate or better both times they will be certified for TLFB. If they have been certified in TLFB for another study, then this step can be skipped. We will randomly audiotape subsequent psychosocial assessment, TLFB, and FORT-A group administrations (≈10%) to assess for drift from the protocol using standardized checklists of required content to cover and ignore in each session (performed by a non-study RA). The Physical Therapy assessment and treatment programs will be manualized and videotaped for protocol fidelity (accepted if at least 90% of required content is covered). PT's and/or PT students will be trained by Dr. Maureen Simmonds, who will also supervise. A random selection (≈10%) of videotapes will be reviewed by a non-study RA to ensure there is no drift from the protocol. Prolonged Exposure (PE) treatment for PTSD (implemented during individual FORT-A individual psychotherapy appointments) will be supervised by Dr. Tabatha Blount who is trained in PE.

Maintaining the blind during assessment certification: As is the case in other STRONG STAR studies, IEs will be trained and certified in assessment using non-study (i.e., clinical) cases. This will allow for a more open dialogue about the assessment process during training with Drs. Blount, C. McGeary, and Simmonds. Fidelity to the intervention will be completed by a STRONG STAR Research Assistant who is not part of this study team using standardized checklists.

Participant adherence to FORT-A treatment. As described above, FORT-A is an

intensive, multi-component program. In order to be adherent to treatment, each participant will need to attend group sessions, individual psychotherapy session, biofeedback sessions, and Physical Therapy sessions. One benefit of incorporating all of these programs into a consolidated, intensive program is an increased likelihood that participants will attend all components. In fact, in the original FORT trial, every FORT participant attended all FORT classes and all PT sessions (with the exception of one who elected to undergo shoulder surgery during his enrollment in the study and ended his participation early). FORT-A classes and PT session have some serial dependency (i.e., individual sessions build on one another), but many can stand alone. FORT-A classes include homework, generally in the form of skills practice. Individual FORT-A psychotherapy includes a 6-session Prolonged Exposure protocol for PTSD symptoms. Prolonged Exposure requires "trauma rehearsal" to promote habituation to traumatic memories. PT for FORT includes group exercise 4 days a week followed home-based exercise on the weekends guided by "flowsheets." All interventionists will be trained in motivational interviewing and problem-solving skills to help maximize patient adherence to study tasks. For this research, "adherence" for each FORT-A component will be defined as follows:

FORT-A Component	Adherence Criterion	Adherence Management
FORT-A Psychotherapy Group (4 days/wk x 3 wks)	10/12 Classes	Make-up missed class in extra individual session
FORT-A Physical Therapy Group (4 days/wk x 3 wks)	10/12 Sessions	Make-up missed PT with +1 flowsheet
Individual Psychotherapy (2 days/wk x 3 wks)	5/6 Sessions	Reschedule missed IP session
Biofeedback (4 days/wk x 3 wks)	2/6 Sessions	Reschedule missed BFB session
Homework: **Group** **Individual Psychotherapy** **PT**	 8/10 practice sessions 4/5 trauma rehearsals 2/2 weekend flowsheets	Give opportunity for practice/trauma rehearsal before class

Study interventionists will maintain study activity logs (see **Appendix E**, maintained centrally by the Study Coordinator) where they will log the date and completion status of each clinical activity (including sessions attended or missed). These will be brought to weekly interdisciplinary staffing meetings where adherence will be discussed and problem-solved by the interdisciplinary treatment. The PI will attend parts of these meetings to monitor study progress and troubleshoot general problems (he cannot stay when specific patients are discussed, even by study ID, because he

would become aware of which IDs are in the FORT-A group). A study activity log example is below:

FORT-A; Week 1				
ID	Date	Activities	Attended?	Notes
10EX1	01/01/2001	Group PT IP	Y Y Y	Patient reported an injury on 01/02/2001; entered in AE log as non-study-related; consulted study MD on 01/05/2001; pt was cleared to continue Patient given an extra flowsheet for the evening of 01/05/2001 to make up that missed session; BFB missed on 01/05/2001 and was rescheduled for next week
	01/02/2001	Group PT BFB	Y Y Y	
	01/03/2001	---- Rest Day ----		
	01/04/2001	Group PT IP	Y N Y	
	01/05/2001	Group PT BFB	Y N N	

Participant adherence to assessments. Adherence to assessments is vital to this work. For this research, assessment is broken into 3 distinct categories (psychosocial, functional, opioid). Most assessments are administered at pre-treatment, post-treatment, 6-month follow-up, and 12-month follow-up. A few measures are ongoing. Adherence to assessment is defined as completion of assessments within a specified window of time. Categories of assessment, assessment windows, and managing adherence to assessments are as follows:

FORT-A Assessment Category	Assessment Window	Tips to Promote Adherence
Psychosocial Assessments **Functional Capacity Assessments** **Opioid Assessments**	Pre-treatment/Baseline *≤ 2 weeks before treatment Post-treatment *≤ 2 weeks after Tx completed 6-month follow-up *24 weeks (±2 weeks) after Tx completed 12-month follow-up *50 weeks ±2 weeks after Tx completed	Schedule pre- and post-tx assessment with first and last days of tx Reminder/check in phone calls every month Psychosocial and FCE scheduled on same day

Ongoing Assessments	MEMS/Actiwatch – Start at pre-treatment and end at 12-month f/u TLFB/MQS – Administered at pre- and post-treatment and every month after post-treatment.	

Study evaluators will maintain active logs for assessments identifying participants by unique ID # only and including date of evaluation, whether or not evaluation was in a study window, if PI approved out of window assessment (when outside of a window), whether an AE was identified in the assessment (e.g., suicidal ideation on the PHQ-9 item #9), and notes about assessment (see **Appendix F**). These logs will be monitored by the PI and coordinator weekly to ensure that assessments are completed on time. An example assessment log is as follows:

ID	Assessment	Assessment Domains	Assessment Date	Window? (Approved?)	Notes
10EX1	Pre-Treatment * within 2 wks before tx phase	Psychosocial FCE TLFB MEMS Actiwatch	01/01/2001 01/01/2001 01/01/2001 01/01/2001 01/01/2001	Y Y Y Y Y	Treatment Phase Start 01/04/2001 End 01/25/2001 10EX1 forgot MEMS and Actiwatch at Post-Tx; PI approved out of window download; we can use data up to 01/25/2001 10EX1 sustained injury playing basketball on 07/20/2001; not cleared for FCE for 3 months; PI denied out of window assessment due to injury delay 10EX1 completed FCE on 01/24/2002 but not time for testing; r/s for when returns from vacation (01/24); PI approved out of window
	Post-Treatment * within 2 wks after tx completed	Psychosocial FCE TLFB MEMS Actiwatch	01/25/2001 01/25/2001 01/25/2001 02/10/2001 02/10/2001	Y Y Y N (Y) N (Y)	
	6-Month *24 weeks ± 2 weeks after tx completed	Psychosocial FCE TLFB MEMS Actiwatch	07/22/2001 --- 07/22/2001 07/22/2001 07/22/2001	Y N (N) Y Y Y	
	12-Month *50 weeks ± 2 weeks after tx completed	Psychosocial FCE TLFB MEMS Actiwatch	02/07/2002 01/24/2002 02/07/2002 01/24/2002 01/24/2002	N (Y) Y N (Y) Y Y	

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Enroll / Screen (W-4 to 0) ≤ 4 Weeks BEFORE Baseline	Randomize (W-4 to 0) ≤ 4 Weeks BEFORE Baseline	Baseline (W0) ≤ 2 Weeks BEFORE Treatment	Post-Treatment (W4-5) ≤ 2 Weeks AFTER Treatment	Six-Month Follow-up (W30) ±2 Weeks of 6-Months Post-Tx	12-Month Follow-up (W56) ±2 Weeks of 12-Months Post-Tx	Lost to Contact OR Dropped From Treatment
Informed Consent Form	X						
Demographics	X						
Health Questionnaire			X	X	X	X†	
Health Questionnaire Addendum			X	X	X	X	
Inclusion/Exclusion Criteria	X						
Enroll/Screen	X						
Randomize		X					
Concomitant Medications			X	X	X	X	X
Adverse Events			X	X	X	X	
Oswestry Disability Index	X		X	X	X	X	X
Quick Drinking Screen (QDS)			X	X	X	X	
Fagerstrom Test for Nicotine Dependence (FTND)			X	X	X	X	
Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco (FTNB-ST)			X	X	X	X	
PROMIS Short Form	X		X	X	X	X	
Timeline Followback Interview	X		X	X	X	X	X
Ohio State University TBI Scale Short Form – VA	X						
Patient Health Questionnaire – 9 (PHQ-9)	X		X	X	X	X	

Assessment	Enroll / Screen (W-4 to 0) ≤ 4 Weeks BEFORE Baseline	Randomize (W-4 to 0) ≤ 4 Weeks BEFORE Baseline	Baseline (W0) ≤ 2 Weeks BEFORE Treatment	Post-Treatment (W4-5) ≤ 2 Weeks AFTER Treatment	Six-Month Follow-up (W30) ±2 Weeks of 6-Months Post-Tx	12-Month Follow-up (W56) ±2 Weeks of 12-Months Post-Tx	Lost to Contact OR Dropped From Treatment
PTSD Checklist – 5	X		X	X	X	X	
Functional Capacity Evaluation			X	X	X	X	
Pain Catastrophizing Scale			X	X	X	X	
Fear Avoidance Beliefs Questionnaire			X	X	X	X	
Chronic Pain Acceptance Questionnaire			X	X	X	X	
Multidimensional Pain Inventory			X	X	X	X	
Generalized Anxiety Disorder – 7 item (GAD-7)			X	X	X	X	
Depressive Symptom Inventory-Suicidality Subscale	X		*	*	*	*	
Current Opioid Misuse Measure			X	X	X	X	
Mini International Neuropsychiatric Interview	X						
Actiwatch			X	X	X	X	
MEMS eCap			X	X	X	X	
Treatment Helpfulness Questionnaire				X			
Subjective Opiate Withdrawal Scale			X	X	X	X	
Pain Diary	X		X	X	X	X	
Interpersonal Needs Questionnaire (Burdensomeness Items)	X		X	X	X	X	
Phone Contact (Adherence / AE / MEMS-Actiwatch)*					X*	X*	
Pregnancy Test	X						

Assessment	Enroll / Screen (W-4 to 0) ≤ 4 Weeks BEFORE Baseline	Randomize (W-4 to 0) ≤ 4 Weeks BEFORE Baseline	Baseline (W0) ≤ 2 Weeks BEFORE Treatment	Post-Treatment (W4-5) ≤ 2 Weeks AFTER Treatment	Six-Month Follow-up (W30) ±2 Weeks of 6-Months Post-Tx	12-Month Follow-up (W56) ±2 Weeks of 12-Months Post-Tx	Lost to Contact OR Dropped From Treatment
Medication Quantification Scale – Version III	X		X	X	X	X	
Prescription Access in Texas						X†	
Missing Data Assessment							X

*Occurs monthly after the post-treatment visit

† To assess opioid prescriptions dispensed for the past year

Figure 3. Flowchart: Recruitment to Randomization

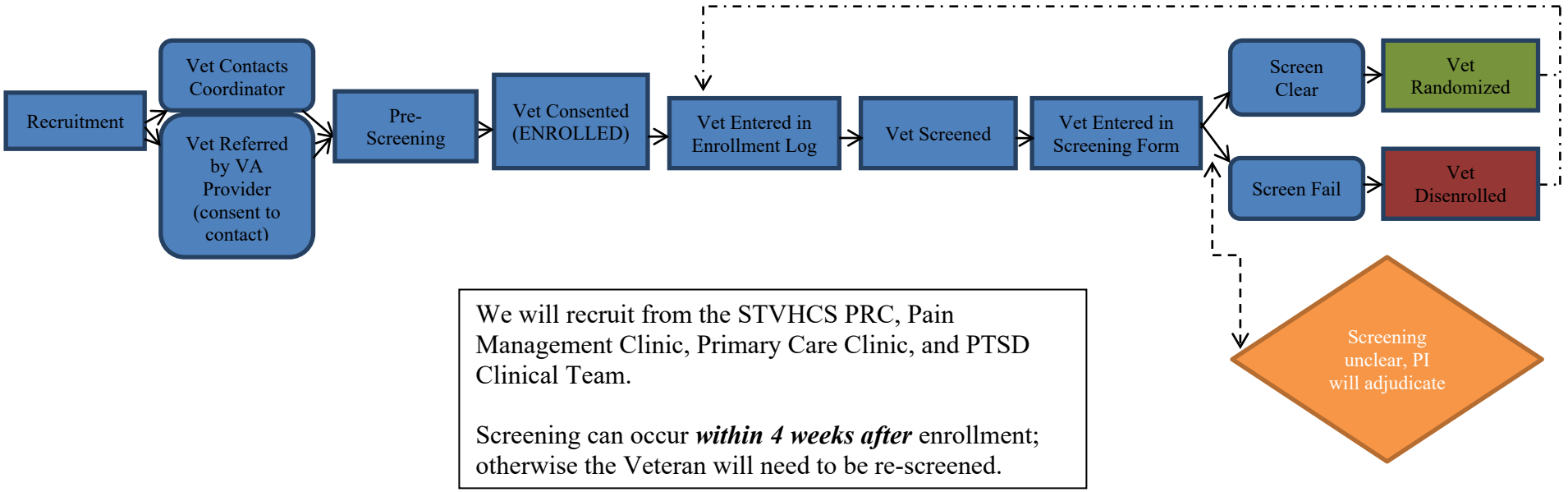
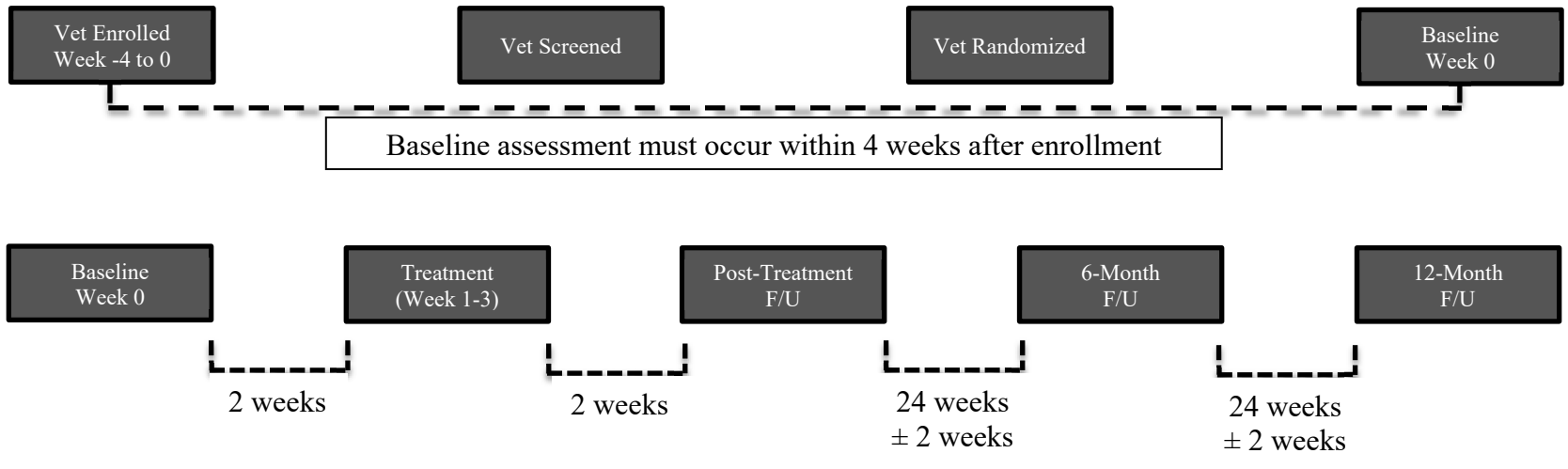


Figure 4. Flowchart: Enrollment to Assessment



6.2 Description of Evaluations

6.2.1 Enrollment and Screening Evaluation (Week -4 to Week 0; See Figure 3)

All screening will occur within 4 weeks after consent (so consent occurs at Week -4)

Consenting Procedure

Potential participants will have the study explained to them in a safe and private location. The Veteran will be given a copy of the informed consent document (ICD) to read. The research team member obtaining informed consent will then engage the Veteran in an interactive explanation of the study guided by the Informed Consent Form. After the Veteran has read the ICD, they will be given the opportunity to consider participation and discuss the research with other family and friends. The Research Team will be available to answer any questions about the research. Once the potential participant has reached a decision, the advising staff member will review the risks and benefits of study participation and ensure the Veteran has an understanding of the material discussed, and the risks and benefits of their potential involvement in the study. The advising staff member will have the participant sign the consent form. A copy of the signed ICD will be given to the Veteran. STRONG STAR addresses issues related to mental capacity of potential participants through ongoing screening procedures using trained independent evaluators. Any concern that a potential participant is unable to comprehend what is being asked of them to participate in the research or the consent document will be referred to a licensed psychologist for additional assessment. Similarly, any concerns identified during the course of the study that participants may no longer comprehend what is being asked of them or be able to engage in the study procedures will be referred to a licensed psychologist and the research team. All Veterans who have provided informed consent will be considered enrolled to the study. Consent will be tracked for each participant using the NCCIH Screening and Enrollment Log (**Appendix A3**).

Screening

All participants will be screened **after** consent (i.e., enrollment) and screening will be tracked by the Coordinator and Research Assistant using the STRONG STAR Screening Form, see **Appendix H**). Initial contact will either be made with the participating Veteran directly (in response to an advertisement of flyer, the Veteran will contact a member of the research team) or on referral from the Veteran's STVHCS provider in the PRC, Pain Management Clinic, PTSD Clinical Team, or Primary Care Clinic. Each clinic where we recruit for this research will be given a list of inclusion and exclusion criteria for this research. After providing informed consent, each Veteran will be screened to confirm their suitability for participation in this research. Those who are found to be ineligible for this research study will be disenrolled from the study as a "screen failure" and this will be tracked using the NCCIH Screening and Enrollment Log. Screening will be completed by an Independent Evaluator (IE) and a Clinical Psychology Fellow or Intern (who will complete the clinical interview). The following assessments, assessment windows, and inclusion thresholds must be completed as part of screening:

Assessments (Inclusion Criterion)	Assessment Window	Inclusion Threshold
Clinical Interview PROMIS – SF (Deployment-Related Chronic Musculoskeletal Pain; CMP)	Within 4 weeks after enrollment	Veteran must report pain that has interfered in daily functioning more days than not for the past 3 months CMP must be related (e.g., exacerbated or cause by) to OEF/OIF/OND deployment Service Member must not be currently engaged in treatment specifically targeting opioid use Veterans not on opioid medication were referred by any of their VA medical providers.
Oswestry Disability Index (Moderate Disability)		Veteran must score ≥ 20% disability for enrollment
Timeline Follow-back Interview (Persistent Opioid Use)		Veteran must report using opioid medication for 20 out of 30 days for the past 3 months
Patient Health Questionnaire - 9 (Moderate Depression or PTSD)		Pain must present in the context of depression (based on a PHQ-9 Score of 10 or more) or PTSD
PTSD Checklist – 5 (Moderate Depression or PTSD)		Pain must present in the context of PTSD (based on a PTSD Checklist Score of 25 or more) or depression
Depressive Symptom Inventory-Suicidality Subscale (No active suicidal ideation or intent)		Veterans cannot enroll if they report suicidal ideation with intent. There is no widely accepted cutoff score for this on the BSSI, so ***any***

		positive BSSI score will need to be reviewed by the PI and Psychologist Co-Investigators and the PI will make a decision on inclusion
Ohio State University TBI Scale Short Form – VA (No severe TBI-related cognitive difficulty)		Veterans cannot participate with severe TBI-related cognitive impairment
MINI (Psychosis Module)		Screen out psychosis
Pregnancy Test		Screen for pregnancy

The outcome of all screening will be briefed to the PI and Co-Investigators during a weekly study meeting (in a de-identified format) for a final determination of each enrolled participant's eligibility for the study. Once confirmed eligible, participants are randomized. The PI will adjudicate any unclear determinations of eligibility for enrollment and the determination will be entered into the enrollment log.

6.2.2 Randomization and Baseline

Randomization (Wk -4 to 0)

Once the PI and Co-Investigators have determined that a participant has satisfactorily met all inclusion/exclusion criteria, the participant will be randomized by the study coordinator (this could be done at any time from week -4 to week 0 as long as consenting and screening come first). The date of randomization will be recorded on the Enrollment Log.

The maximum allowable time between enrollment and randomization is 4 weeks. If screening and determination of eligibility goes beyond this allowable window, the participant will need to be re-screened before randomization.

Baseline Assessments (Week 0; See Figure 4)

Baseline assessment occurs within 4 weeks from the time of enrollment (regardless of when baseline assessment occurs relative to screening, Baseline Assessment is identified as Week 0).

For participants who have successfully been screened for eligibility and are randomized into the study, baseline assessments are performed to measure the study outcomes. They also ensure that the groups are balanced with respect to baseline characteristics.

Baseline evaluations for this study include:

Assessments (Domain Assessed)	Assessment Window	Special Instructions

Health Questionnaire / Addendum (previous pain treatments) (comorbid pain/medical conditions)	≤ 2 weeks before treatment start	**Balance Sample** Past medical history will not change, so this measure is only given once
Concomitant Medications and Medication Quantification Scale-III (medications that may impact pain) (medications that may impact mood)		**Control: Other Medications** Medications may change, so this will be assessed at all assessment visits; self-report and CPRS review
Timeline Follow-back Interview (opioid & other pain medication use)		**Endpoint: Hypothesis 3** Assessed at all assessment visits
Oswestry Disability Index (self-report disability)		**Endpoint: Hypothesis 1** Veterans cannot participate with moderate to severe TBI-related cognitive impairment
PHQ-9 (depression symptoms)		**Endpoint: Hypothesis 2** Assessed at all assessment intervals
PTSD Checklist – 5 (PTSD symptoms)		**Endpoint: Hypothesis 2** Assessed at all assessment intervals
Depressive Symptom Inventory-Suicidality Subscale (DSI-SS) (suicidal ideation or intent)		**Risk Surveillance** Suicide risk is not a research endpoint, but if suicide risk is present at a previous assessment (e.g., any positive response for BSSI screening items) then BSSI will be repeated at the next assessment interval (unless participant is disenrolled for a VA mental health treatment referral)
Functional Capacity Evaluation (objective disability)		**Endpoint: Hypothesis 2** Assess at all assessment intervals
Pain Catastrophizing Scale (pain-related cognitions)		**Endpoint: Hypothesis 2** **Variable: Exploratory**
Interpersonal Needs Questionnaire (Burdensomeness)		**Endpoint: Hypothesis 2** **Variable: Exploratory**
Fear Avoidance Beliefs Questionnaire		**Endpoint: Secondary Objectives** **Variable: Exploratory**
Chronic Pain Acceptance Questionnaire		**Endpoint: Secondary Objectives**

		Variable: Exploratory
Multidimensional Pain Inventory		**Endpoint: Secondary Objectives** **Variable: Exploratory**
Generalized Anxiety Disorder- 7 item		**Endpoint: Hypothesis 2** Assess at all assessment intervals
Current Opioid Misuse Measure		**Endpoint: Hypothesis 4** Assess at all assessment intervals
Actiwatch		**Endpoint: Hypothesis 2** Assess at all assessment intervals
MEMS eCap		**Endpoint: Hypothesis 4** Assess at all assessment intervals
Treatment Helpfulness Questionnaire		**Endpoint: Secondary Objectives** **Variable: Exploratory** Only given post-treatment
Subjective Opiate Withdrawal Scale		**Endpoint: Hypothesis 4** Assess post-treatment and at follow-ups
Pain Diary		**Endpoint: Hypothesis 2** Assess at all assessment intervals
Phone Contact (Adherence/AE/MEMS/Actiwatch		**Treatment Adherence** Occurs at all assessment intervals
Quick Drinking Scale (QDS)		**Common Data Element with STRONG STAR Studies**
Fagerstrom Test for Nicotine Dependence (FTND)		**Common Data Element with STRONG STAR Studies**
Fagerstrom Test for Nicotine Dependence – Smokeless Tobacco (FTNB-ST)		**Common Data Element with STRONG STAR Studies**

Randomization

As noted above, participants will be randomly assigned to the FORT-A or PRC on a 1:1 allocation ratio using a randomly selected block size with randomly permuted assignments within blocks.

In the original FORT study we found that the ideal treatment group size for each iteration of the program was 5 participants (though successful groups were able to run with as few of 3 members and as many as 7). Thus, we will attempt to fill treatment

cohorts for FORT-A and PRC with between 3 to 7 participants (as described in Efrid, 2011). The coordinator and co-coordinator will be blinded to all randomization assignments but will initiate a treatment cohort when a sufficient number of participants have been assigned.

There is a four-week window between enrollment and baseline assessment (Week -4 to Week 0, as shown in 6.1). Study intervention must begin within 2 weeks after baseline to ensure that baseline assessment data adequately represent *current* functioning at the time of treatment, especially functional capacity evaluation [FCE] data that are used to guide the physical therapy portion of the interdisciplinary intervention. Test-retest reliability of FCE has been confirmed over a period of two weeks (Brouwer et al., 2003), with only slight fluctuations in more frequent testing resulting in a slight increase in lifting capacity if repeated across two days, likely due to practice effects (Reneman et al., 2002). Thus, intervention will generally begin within 5 weeks of enrollment.

6.2.3 Blinding

Blinding in an interdisciplinary behavioral intervention is extraordinarily difficult since the intervention requires face-to-face contact and continuity of an interdisciplinary approach requires different interventionists to be able to talk to one another about patient progress. This is particularly true in trials of openly symptomatic conditions (like chronic pain; see Friedberg, Lipsitz, & Natarajan, 2010). There is no placebo control for an intervention like this (nor would the VHA allow one), so blinding is best accomplished through careful consideration of "need to know" privileging. Figure 2 provides a visual representation of who needs blinding and who is allowed to maintain awareness of patient identity. The entire study staff will be thoroughly briefed on the importance of maintaining blinds and the study coordinator will attend all study meetings and help ensure that blinds are maintained when blinded and unblinded personnel discuss the study participants. We have chosen to use a multi-level blinding scheme (as described by Friedberg et al.) in which study personnel will be blinded to randomized treatment **condition**, assessment **outcomes**, or **both** (as shown in Figure 2).

Study interventionists and their supervisors (for group psychosocial treatment; individual psychotherapy; biofeedback, and physical therapy) cannot be blinded to **condition** because they will be aware of the treatment condition of the patients they treat. Research Assistants (RA's), blinded to participant identity, will listen to audio recordings of treatment sessions and will rate adherence to the treatment manual using a standardized checklist (see Section 10.3 Quality Assurance) for more information about this. The Research Coordinator and Co-Coordinator will be aware of participant condition (because they are responsible for randomizing and because they need to assist with adverse events monitoring and administrative oversight of treatment and assessment procedures), but they will be blinded to **outcomes**. The Coordinator and Co-Coordinator will not be directly involved in treatment or assessment and will be asked to only refer to participants by their unique identifiers when discussing participants with RA's, the PI, or IE's. Independent Evaluators will

become aware of outcomes during the course of their assessments, but will be blind to **condition** of the participants they assess.

6.2.3.1 Maintaining Blinds

During treatment sessions, interventionists are asked not to refer to the participant by name and all quality assurance audio files are labeled only with the date of intervention, the session number, and the unique study identifier for the participant(s) involved. Because it is possible that the Research Assistant (RA) completing quality assurance may become aware of the identities of participants in the individual or group treatments, RA's who complete quality assurance will not take part in outcomes assessments (which will only be completed by Independent Evaluators through STRONG STAR).

Independent Evaluators will enter participant data from assessments directly into the secure STRONG STAR SQL Database using standard STRONG STAR operating procedures (see STRONG STAR Data Entry SOP, Appendix I).

** The PI and study physicians (Dr. Jaramillo, Dr. Eapen) will sit in on weekly interdisciplinary staff meetings with study interventionists to discuss the progress of all study participants (both FORT-A and Treatment-As-Usual) during which participants will be discussed by case number only.

6.2.4 Followup Visits (see Figure 4)

Follow-up assessments will occur in the following intervals:

Visit	Measure	Assessment Window
Visit 2 (Baseline)	Psychosocial Assessment Pain Diary Functional Capacity Evaluation (FCE) Upload Actiwatch Provide and Train for MEMS Adverse Events Opioid/Medication Assessments (TLFB/SOWS/COMM/Concomitant Medications) MQS STRONG STAR Common Data Elements	≤ 2 weeks **before** treatment
Visit 14 (Post-Treatment)	Psychosocial Assessment Pain Diary FCE	≤ 2 weeks **after** treatment

	Upload Actiwatch Upload MEMS Adverse Events Opioid/Medication Assessment MQS STRONG STAR Common Data Elements	
Phone Assessments 1-11	Opioid/Med Assessment (TLFB) MQS	Monthly ±1 week
Visit 15 (Six-Month Follow-Up)	Psychosocial Assessment Pain Diary FCE Upload Actiwatch Upload MEMS Adverse Events Opioid Assessment/Medication MQS STRONG STAR Common Data Elements	± 24 weeks after treatment ±2 weeks

6.2.5 Completion/Final Evaluation

List each assessment to be performed at the participant's final visit.

Visit 16 (One-Year Follow-Up)	Psychosocial Assessment Pain Diary FCE Upload Actiwatch Upload MEMS Adverse Events Opioid/Medication Assessment (including CPRS and PAT) MQS STRONG STAR Common Data	± 50 weeks after treatment ±2 weeks

	Elements Exit Interview	

All participants will be asked to complete all final assessments, regardless of whether or not they complete the study. After completing the intervention, we will maintain monthly telephone contact with all participants to promote adherence to follow-up assessments and to give them an opportunity to report any adverse events they may have experienced since finishing the three-week intervention phase. This monthly contacts will also include monthly administration of the TLFB for pain medication and opioid medications and administration of the MQS. We will also use these monthly calls to identify and troubleshoot any potential problems with the Actiwatch or MEMS Caps.

Participants who were lost to contact at any point before the 12 month follow-up assessment will be contacted to complete the Missing Data Assessment, ODI, TLFB and Concomitant Meds Form. Participants will be mailed a letter explaining why they are being contacted, how long the phone interview will take, and what information we will collect. The letter will also include opt-out information. Within two weeks of the participants receiving this letter, we will contact participants to discuss whether they would like to participate. The Missing Data Assessment is a 4-item measure of global symptom improvement of pain, perception of satisfaction and burdensomeness of study treatments, and reason(s) for discontinuing study participation. This assessment will be used to assess missing data randomness and to categorize participants who discontinued study participation as a way to help impute missing data and improve future studies with these treatments in similar populations.

7. SAFETY ASSESSMENTS

Upon enrollment, all participants will be monitored for relevant risks through adverse events monitoring protocols (guided in part by the STRONG STAR AE SOP (see **APPENDIX J**). For this study, there is risk for adverse events related broadly to psychological distress, physical injury, and opioid withdrawal.

7.1 Specification of Safety Parameters

Section 7.3 of this protocol describes a number of formal assessment measures and related safety thresholds. Along with these formal assessment measures, we will also assess pain intensity ratings for each participant before and after each session of study-related Physical Therapy. The PI published a study of pain intensity ratings in functional restoration programs and noted that participants who reported pain on a 0-10 Numeric Rating Scale between 8-10/10 generally demonstrated worse outcomes after treatment. Thus, individuals reporting pain after PT sessions with pain ratings between 8-10/10 will be assessed for safety by Dr. Simmonds or a PRC PT/OT and discussed with the PI (using unique identification number).

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Adverse Events tracking is highly recommended for pain research based on IMMPACT recommendations (Turk et al., 2003) and will be tracked, monitored, and adjudicated for this research in accordance with **Appendix J**. Physical Therapy and Psychotherapy treatment providers will maintain regular clinical notes input within 24 hours of each appointment into the VA Electronic Medical Record (in accordance with **Appendix K**). These data will be discussed and analyzed during the weekly research meeting with the PI and Co-Investigators during which the risk profile will be determined and addressed.

Behavioral health interventions for chronic pain tend to be safe compared to medical interventions (Morley et al., 1999). Although there are data describing the adverse effects associated with introducing opioid medications to a pain management program (see Moore & McQuay, 2005), there is little in the extant literature describing the risks of opioid sparing in the context of a program like the OSI (including risk for opioid recidivism and withdrawal symptoms). Indeed, data from the original FORT trial did not reveal any adverse consequences of opioid reduction among those who voluntarily suspended opioid medication use.

A comprehensive review of Physical Therapy outcomes among military PT service recipients covering 472,013 PT visits across 40 months revealed no significant adverse effects of PT for active duty and Veteran patients seeking PT services (Moore et al., 2005). However, Carlesso and colleagues (2010) suggest that this negative finding is likely a function of poor adverse event surveillance in research utilizing PT. The STRONG STAR Consortium recently published a description of Adverse Events monitoring guidelines and recommendations for behavioral health trials including a PTSD diagnosed population (Peterson et al., 2013). These recommendations have been incorporated into the risk monitoring procedures used for the proposed study.

7.3 Adverse Events and Serious Adverse Events

*An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recording regardless of their relationship to the study intervention.*

*A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.*

AEs and SAEs may be related directly to research participation or unrelated to research. Potential research-related AEs and SAEs for this study include the following:

	Adverse Event	Serious Adverse Event

Research Related	Increased PTSD symptoms Increased pain intensity Increased emotional distress Opiate withdrawal symptoms	Increased Suicidal Risk Hospitalization for mood or pain
Research Unrelated	Example: Flu	Example: New Injury

All AE and SAE monitoring will be completed using the STRONG STAR procedures for Adverse Events Monitoring, Documentation, and Adjudication (**Appendices J, L, and M**). Any study member who identifies an AE or SAE will immediately report it to the study coordinator and begin the process for prompt reporting to the IRB pursuant to the SOP. SAE and AE report forms (see attachment SOPs) will be forwarded to STRONG STAR Regulatory Personnel who will prepare the official report to the IRB. Each participant chart includes an AE/SAE tracking form in which AEs and SAEs will be documented by hand as soon as they are identified (per the SOP)

Adverse events will be monitored through the following mechanisms:

AE/SAE	Assessment Tool	Notes
PTSD Symptoms	PCL-5	Given at every assessment interval and at every individual PTSD treatment session for FORT-A participants Clinical significant change for the PCL-5 has not yet been established, so we will use a 20-point increase in symptoms as a clinically significant indicator of PTSD symptoms (based on the previous version of the PCL; see **Appendix N**)
Pain Intensity	Numeric Rating Scale (NRS)	Assessed at every assessment interval and at every physical therapy appointment for FORT-A participants Opinions vary on a clinically meaningful change in pain numeric rating, but many agree that an increase in pain rating > 2 points is clinically significant (see McGeary et al., 2006)
Emotional Distress	PHQ-9	Given at every assessment interval and once a week during group treatment

		sessions for FORT-A participants Change in PHQ-9 scores is clinically significant if the total score rises above 15 (as defined in Kroenke & Spitzer, 2002). Those who begin the study with a score above 15 show significant change (requiring AE report) if the score rises 5 points or more. If item #9 increases at all, this will be reported an AE. An increase of Item #9 by 2 points or more will be considered a SAE.
Opiate Withdrawal	SOWS	The Subjective Opiate Withdrawal Scale will be given to all FORT-A participants once a week during treatment and at all assessment intervals for all follow-up intervals. A SOWS score of 11 or more will indicate an AE requiring follow-up (based on established cut-off scores).

Turner JA, Mancl L, Huggins KH, Sherman JJ, Lentz G, LeResche L. Targeting temporomandibular disorder pain treatment in hormonal fluctuations: A randomized clinical trial. Pain 2011;152:2074-2084.

This study maintains a weekly research meeting (starting September 2015; currently set for Thursday morning from 1030-1100 at the STRONG STAR Conference Room with an open phone line for those who need to call into the meeting) to discuss research progress and to discuss participant status and flow throughout the research process. All Adverse Events (AEs) and Serious Adverse (SAEs) will be discussed at these meetings (attended by all study staff). To protect blinding, participants will be discussed by unique identifier only.

AE reporting procedures (as described in the attached SOP) will begin immediately after an AE is noticed and will be reported to the IRB after discussion at the weekly research meeting. SAEs must be reported to the IRB within 24-48 hours. If a protocol deviation, SAE or UPIRSO is not reported within 48 hours, a reason will need to be documented on the P50 form.

7.4 Reporting Procedures

Reporting procedures for all AEs and SAEs are described in **Appendices J and L** (STRONG STAR Adverse Events SOP). The P50 reporting template (included with the SOP Appendix J) will be used to document all AEs and to record their classification and reporting timelines. The severity and research relatedness of AEs and SAEs will be determined by the study PI (Dr. Don McGeary) pursuant to the STRONG STAR Adverse Events Adjudication SOP (**Appendix M**).

7.5 Followup for Adverse Events

If an adverse event does not require disenrollment and referral to VA physical or mental health services, then the research team will offer adjunctive services for attrition prevention as outlined in the STRONG STAR ASAP SOP (**Appendix O**). Adjunct services and attrition prevention (ASAP) involves the structured provision of extra adjunctive psychotherapy or medical consultation services designed to mitigate risk of adverse events and maintain participants on protocol (within the limits of good ethics and clinical practice). ASAP sessions can be prompted by the participant, an IE, or an interventionist. These sessions are defined in the SOP as "any out of protocol contact (in person or by telephone) lasting longer than 20 minutes. Each participant is allowed three ASAP sessions during protocol intervention. If more intervention is needed, or the PI believes that a higher level of intervention is needed, then the participant will be dropped from protocol treatment and referred for appropriate intervention in the VA. For participants remaining on protocol with ASAP or referral services, progress will be briefed to the PI daily to monitor progress. When the participant and provider report resolution or stability of symptoms, the participant will be re-assessed with the index measure (e.g., PHQ-9 for depression, NRS for pain) and the results will be discussed with the PI (using only the unique identifier for the participant to maintain blinding) for a final determination of resolution and continuation on protocol.

Please note that STRONG STAR maintains a separate SOP for the monitoring, management, and intervention of suicide risk in study participants (as detailed in **Appendix P**). As detailed in the Suicide Risk SOP, all study staff are thoroughly trained in suicide risk assessment, with formal assessments overseen by a licensed psychologist. This SOP describes specific algorithms for risk level determination and pathways for intervention, follow-up, and implications for research involvement.

7.6 Safety Monitoring

STRONG STAR does maintain a SOP for External Monitoring of all consortium studies (see **Appendix Q**). This has been attached for NCCIH's information, and safety will be monitored in a manner consistent with standard STRONG STAR practice and will be overseen by the STRONG STAR DSMP.

8. INTERVENTION DISCONTINUATION

There are few reasons for discontinuing any participant from this study. However, under certain circumstances, it may be necessary to buttress study-related treatment to stabilize temporary conditions needing immediate intervention. The STRONG STAR Research Consortium has established an Adjunctive Services and Attrition Prevention (ASAP) policy (see **Appendix O**) describing a preliminary step for intervention in which a distressed participant will be allowed three out-of-protocol intervention sessions (with their individual or group psychotherapist) of 20 minutes or less to stabilize their condition. Should a pre-determined recovery criterion be met (it is impossible to predict all potential emergencies and goals are determined by committee as described in the ASAP SOP), then the participant will remain enrolled in the study. If recovery is not achieved, then the research team (led by the PI) will

decide on whether the participant should be retained. Those requiring a referral for services outside of the study (i.e., if ASAP is not sufficient for symptom management) will be referred to the appropriate services based on the STRONG STAR Suicide Risk SOP (**Appendix P**), through the VA Hospital (i.e., STVHCS), or using the San Antonio area referrals as described on the STRONG STAR Referral Form (**Appendix R1**). All participants referred for services outside of the study protocol will be tracked using the STRONG STAR Referral Form (**Appendix R2**). If a participant needs to be screened for safety when he/she is outside of the immediate San Antonio area, a distance assessment will be completed as described in **Appendix R3**. The following are examples of conditions/circumstances subject to the ASAP process (all of which would qualify as AEs and be tracked/documented accordingly):

1. *Presence of Suicidal Ideation*: If suicidality is identified during the course of study participation, it is vital that this be addressed and stabilized as quickly as possible. Suicide risk will be monitored, classified, and acted-upon based on the STRONG STAR Suicide Risk SOP.
2. *Physical Injury during PT:* If a participant sustains an injury during PT, Dr. Simmonds will collaborate with Dr. Eapen or Dr. Jaramillo to determine if brief ASAP intervention will help restore function and allow continuation of the study protocol.
3. *Exacerbation of PTSD or Depression Symptoms:* In any study involving the treatment PTSD, there is a chance that emotional distress may temporarily worsen. If this happens, adjunctive treatment will be provided using the ASAP protocol.
4. *Opioid Withdrawal Symptoms:* During the course of this study, some participants may choose to stop taking opioid medications (though this is not mandatory), which is increasingly likely in light of recent federal changes to VA prescription practices and the VA's Opioid Safety Initiative. Those who discontinue persistent opioid use may report adverse symptoms of opioid withdrawal that will be monitored at all individual, group, and assessment appointments. Should these symptoms be identified, Dr. Eapen and/or Dr. Jaramillo will be notified. They will meet with the PI to discuss if these symptoms can be reasonably addressed under the ASAP protocol.

Participants will continue to be followed with their permission if study intervention is discontinued. There will be no modifications to the schedule and duration of continued followup if the participant is referred to the VA system for treatment and stabilization (though we will ask permission for frequent checks with the participant on their status to ensure that they are doing well and recovering). They will still be asked to complete all measures at all remaining follow-up intervals.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Primary Hypothesis: FORT-A participants will demonstrate significantly greater improvements in self-reported than those receiving PRC treatment as usual (TAU).

"Greater improvement" is defined in this study as statistically significant ***lower*** ODI scores for FORT-A compared to TAU at one-year post-treatment follow-up controlling for differences in ODI at pre-treatment. Logic for selection of ODI as the primary outcome is described in Section 3 of this protocol. Validity and reliability of the ODI has been well-established in over 100 published studies, and use of the ODI will allow comparison of the proposed study results to numerous other pain populations and interventions (allowing for better prediction of result generalizability outside of the population of interest; Fairbank et al., 1980; Fairbank & Pynsent, 2000).

Study Design and Rationale: To test the primary hypothesis, the proposed research needs to simply determine that the experimental intervention (FORT-A) is superior to treatment as usual. The unique requirements of the VA and DoD systems preclude a truly controlled trial (i.e., military and VA IRBs will not approve research denying access to treatment for their covered constituents). Thus, FORT-A cannot be compared to a no-treatment control condition. Because of the variability in chronic pain intervention in the VA system, definition of treatment-as-usual can be difficult. In the original FORT trial, we chose to compare the FORT program to the best available intervention that the DoD had to offer for chronic pain. If FORT was truly an innovative and high-impact intervention, then it should be better than anything else that the military was using to manage chronic pain. Similar logic applies to the present study. FORT-A was developed to improve upon the original FORT program for application to a more complex patient population than that treated in the FORT study. Fortunately, the best available intervention for complex chronic pain in the VA right is through the Polytrauma Rehabilitation Center, making the PRC a natural comparator for this study. Better yet, the PRC is a structured, interdisciplinary program in which all enrolled participants have access to PT services and an interdisciplinary treatment team. If FORT-A is a truly innovative and high-impact intervention, then it should out-perform the PRC (which has openly expressed difficulty in managing chronic pain; Strasser et al., 2008; Clark et al., 2009; Friedemann-Sanchez et al., 2008). Thus, the most parsimonious design for this research is a two-arm, randomized clinical trial comparing 3 weeks of FORT-A to 3 weeks of PRC intervention. After completion of the three week intervention phase, all participants will be permitted to seek additional treatment through the VA system (which is mandated by the VA IRB). We will track treatment engagement through a review of the VA electronic medical record (CPRS, to which all study team members will have access) and interviews with participants at all follow-up assessment intervals.

Secondary Hypothesis: FORT-A participants will demonstrate significantly lower rates of opioid recidivism than TAU participants at one-year post-treatment. Opioid and other pain medication use is being assessed using a timeline follow-back interview and MEMS caps (with the timeline follow-back as the primary measure based on its documented reliability and validity; Sobell & Sobell, 1992).

- ***We are currently discussing the value of adding urine tox screens at pre-treatment, post-treatment, and one-year follow-up.*** The study team previously eschewed the use of a urine tox screen for this research endpoint

because of concerns about the validity and sensitivity of urine tox screens for opioid use. However, in consultation with Dr. Dawes and the VA Opioid Safety Initiative, we have identified certain tests applied to a urine sample that can reliably and validly illuminate opioid use patterns. We are still examining this addition and how we might be able to partner with the VA to add this to our outcome battery (after discussing this with NCCIH more, of course) without additional cost. The VA system has increased implementation of urine tox screens for opioid using Veterans (see http://www.veterans.senate.gov/imo/media/doc/VA%20Clancy%20Testimony%203.26.20151.pdf). However, studies in the PRC population using urine tox screening risk high attrition because Veterans may feel mistrusted. Because timeline followback has shown reliability and validity in the past, we have chosen to stay with this method for tracking opioid use and recidivism to opioid use. However, we will have access to electronic medical records (CPRS) to identify new opioid prescriptions in the VA system and Dr. Eapen and Dr. Jaramillo can access the *Prescription Access in Texas* website (see https://www.texaspatx.com/Tutorial/Doc/PATIIFAQs.pdf), the Texas State prescription monitoring program, to identify opioid prescriptions dispensed outside of the VA. We are able to keep all opioid medication use confidential as part of the research record and hope that this will increase the reliability and validity of reporting.

Tertiary Hypotheses:

- We plan to use mixed effects hierarchical regression with polynomial change parameters to assess differences in change trajectories for variables related to physical function (functional capacity evaluation, Actiwatch), psychosocial functioning (PHQ-9, PTSD Checklist), and pain variables (Pain Acceptance Questionnaire, Pain Catastrophizing Scale, Pain Intensity Rating). All of these measures were used in the previous FORT study with established reliability and validity.

Exploratory Hypothesis: Based on the PI's ESCAPE trial, we will evaluate the contribution of perceived burdensomeness and pain-related helplessness as potential mediators of the study's primary and secondary endpoints. A subsequent analysis of the ESCAPE data (currently in preparation for publication) has also shown that depression symptoms may mediate these outcomes as well.

9.2 Sample Size and Randomization

The study is powered to detect a clinically meaningful difference between the two intervention groups on the primary outcome (ODI score) at the 12-month follow-up time period. This endpoint was chosen as it represents the durability of the treatment effect and best reflects the potential utility of the FORT-A program for improving the life of patients. The effect sizes used in the calculation are based on our previous FORT trial, for which treatment effects in the FORT study arm were maintained at the one-year follow-up.

Although Aim 2 changed in September 2015, it is important to note that the study must be powered for Aim 1 for two reasons. First, Aim 1 represents the most immediately relevant clinical endpoint, demonstrating that the FORT-A program is clinically superior to Treatment As Usual in this complex patient population. Second, the PI's previous military FORT study revealed a significant decrease in opioid medication use for program completers (compared to TAU). The resulting data suggest that improved pain management through functional restoration is a likely mechanism opioid medication reduction in military pain populations. Thus, Aim 1 must be met to maximize between-groups differences in Aim 2.

To best assess Aim 2, we have chosen to assess medication (opioid and non-opioid) use on a monthly basis (during follow-up assessments and monthly phone calls) using the TLFB and the MQS. The increased frequency in assessment (each measure will be given 12 times) will provide ample power to detect between-groups difference in opioid recidivism over the 12-month study period. Assuming a sample size of N = 130 (n = 65/group), 12 data collection periods (monthly follow-ups for one year), and a statistical significance level of 0.05, the analysis will have power = .80 to detect a clinically meaningful difference between the study groups. For example, if the control group exhibits a recidivism rate of 45% (as suggested in Section 2.1 of this document) and the active treatment group exhibits a recidivism rate of 22.5%, the study will have power = .80.

We will enroll n = 65 (N = 130) and anticipate <= 30% all-source attrition rate as in our previous study. Assuming that at the 12-month follow-up the standard care treatment arm will report mean (SD) ODI scores of 19.5 (6.6), using a two-tailed α = 0.05, we will have power = 0.80 to detect effect sizes as small as d = 0.50. For the ODI, this is equivalent to a clinically meaningful 3.3 point difference between groups. In our original FORT trial, we observed a 9.2 point difference between individuals who were not lost to follow-up at 12-months. Thus, for the intention-to-treat analyses, where we expect that up to 30% of individuals will require imputation of some kind, our expected effect sizes can be attenuated by ~ 60% with sufficient power to detect a clinically meaningful difference. Differences smaller than 3.3 points on the ODI are unlikely to be clinically meaningful.

Treatment Assignment Procedures

Participants will be randomly assigned to each of the study arms based on the rationale and procedures outlined in sections 6.2.2 and 6.2.3 of this protocol. Masking will be managed using the diagram shown in Figure 2. Pursuant to this diagram, masking will be overseen and maintained through a collaboration between the study coordinator (who will not be blind to any part of this study to all for better tracking of participant flow and AEs; though the Coordinator will not take part in any evaluations and is forbidden to discuss blinded information with any study team member without first discussing it with the PI and the STRONG STAR Administrative Core) and the STRONG STAR Data Core (which maintains the link between identity and participant number). Masking of treatment arm to the participant or provider is absolutely impossible in a behavioral trial. Plans for

retention of the blind are described in sections 5.2, 5.4, and 6.2.3.1 of this protocol. If a blind must be broken (e.g, to protect the safety of a participant), then the blind can only be broken by the study Coordinator and/or Co-Coordinator after consultation and permission from the PI and the STRONG STAR Admin Core. To break the blind, the Coordinator will contact the STRONG STAR Data Core and request revelation of the participant identity and linked unique identifier.

9.3 Definition of Populations

For this study, the per-protocol population will include all participants who completed all assessments and interventions with no major protocol deviations (as defined by Gupta, 2011). The primary analysis will be conducted on the Intent-to-Treat (ITT) population that will include all randomized participants who have completed baseline assessments. .In the original trial, all FORT completers participated in all assessments, but approximately 20% of Treatment as Usual participants were lost to follow-up. Analysis of baseline data revealed that most missing data were missing at random.

9.4 Interim Analyses and Stopping Rules

Interim analyses will not be completed as part of this research. We were fortunate to have solid data from the original FORT trial to help estimate power for the proposed research, and the resulting power analyses are solid. Thus, we do not anticipate uncovering changes in the primary outcome that would necessitate a need for early stoppage or futility of the proposed research and do not feel that we have any preliminary impetus for spending alpha in pursuit of these interim analyses. In conclusion, we do not anticipate observing evidence for early futility or superiority in this trial until all data are gathered in accordance with our in-place power analysis.

The interventions used in this study have been thoroughly studied in other research and it is predicted that the need for a safety review will be low. However, there are some circumstances that would require suspension of study activity and review of safety by an ad hoc safety review committee as follows:

- This is one of the first studies of an interdisciplinary pain program for chronic pain and trauma polymorbidity. The PIs STRONG STAR Pain and PTSD Study revealed no significant exacerbation of PTSD symptoms in a combined pain and PTSD protocol, but PT was not involved in that protocol. There is no reason right now to believe that Physical Therapy will exacerbate PTSD symptoms, but if this were to occur (based on a 20 point increase on the PCL-5) then a safety review would be needed to determine if the study must stop. This finding would also need to be adjudicated through the AE process.
- As noted above, opioid withdrawal effects will be monitored, and a score above 11 on the SOWS will require safety review.
- If physical injury or emotional disruption AEs accumulate (more than 4 minor; easily recovered within one day – or 2 major; requiring more than ASAP intervention to stabilize) then a safety review will be in order.

Such findings are presented to the study statistician or to the Independent Monitoring Committee (IMC) statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician reports his findings to a closed session of the IMC or to the Safety Officer and/or NCCIH. The findings are used to determine what steps will be taken.

9.5 Outcomes

9.5.1 Primary Outcome

The primary outcome for this research is self-reported disability based on the Oswestry Disability Index (ODI). The ODI is a ten-item self-report disability measure assessing an individual's perception of limitation in a number of different life domains due to pain. Each of the ten items asks the participant to use a 0 to 5 numeric rating scale (each with a specific anchor) to rate the extent to which they feel that their functioning is restricted because of their pain. To score the measure, the individual score for each item is summed into a total score and the total score is then divided by 50 and multiplied by 100 to generate a total score ranging from 0 to 100. This total score represents a % disability score which can be categorized as Minimal (0-20%), Moderate (21-40%), Severe (41-60%), Crippled (61-80%), or Bed Bound/Exaggerating (81-100%). The ODI has been cited over 200 times in the scientific research literature with firmly established validity for self-report disability due to chronic pain (Fairbank & Pynsent, 2000). The original ODI (a measure specific to spinal pain) has been updated in Version 2.0 to include extremities in the instructions allowing the measure to validly assess spinal and extremity pain-related disability (Roland & Fairbank, 2000). When compared against the Roland-Morris Disability Questionnaire (another gold-standard spinal disability measure that has been successfully adapted to include extremity pain), the ODI has shown better sensitivity to change at higher levels of disability and is the better measure for this research (Roland & Fairbank, 2000). The ODI can be completed in 5 minutes and scored in one minute.

The ODI will be given at every assessment encounter including screening and will be administered by an IE who is blinded to the randomized condition of the participant. Because this measure is a straightforward, self-report assessment, there is hardly ever a need to adjudicate responses and scoring. However, in some circumstances (e.g., an item is left blank, selection of a response is not clearly marked or covers more than one response) a response will need to be adjudicated between the IE, the Coordinator, and the PI. Meetings for adjudication will occur on an as-needed basis and the Coordinator will ensure that testing materials are not identifiable before discussion with the PI (all assessments will be recorded using only the participant's unique identifier). Adjudication will need to occur within 2 business days from the time that an aberrant or unclear response is noted.

Among the numerous options for pain-related disability assessment, the Oswestry was chosen because of its strength as a predictor of long-term outcome in the original FORT trial and the attention this measure has received in back pain research. The original FORT trial included many outcome measures. Measures of functional capacity were

most responsive to changes (which makes sense based on FORT's emphasis of function over palliative pain control). We compared 4 functional measures (Floor-to-waist lift [FTW], waist-to-eye level lift [WTE], Oswestry Disability Index [ODI], Million Visual Analog Scale [MVAS]). Of the 4 measures, the ODI produced the strongest correlation to other measures of pain management and adjustment.

Pearson correlation between 4 disability measures and other notable FORT outcomes				
r-value	Floor-to-Waist Lift	Waist-to-Eye Lift	Oswestry Disability Index	Million Visual Analog Scale
Depression	-.174	-.278	.690	.424
Fear Avoidance	-.106	-.184	.622	.530
Pain Rating	-.099	-.219	.856	.816

9.5.2 Secondary Outcomes

There are numerous secondary outcomes for this study that can be meaningfully categorized as physical measures (functional capacity evaluation, Actiwatch), medication (MEMS, timeline followback interview, MQS), psychosocial pain (Pain Catastrophizing Scale) and psychosocial trauma and emotional distress (measures of PTSD, depression, suicide risk, etc.). Because these measurement categories all require separate skillsets for interpretation of problematic or ambiguous results, they must all be adjudicated through separate subcommittees within the study team and the STRONG STAR Consortium as follows:

Physical Measures will be adjudicated by the PI, the Research Coordinator, and Dr. Maureen Simmonds (an internationally-recognized expert in Physical Therapy assessment for chronic pain) or a PRC PT/OT. Functional Capacity Evaluation (FCE) data will be recorded by UTHSCSA PT students and/or PRC PT/OT providers and will be discussed with Dr. Simmonds or a PRC PT/OT within two business days after each assessment. Data will be scrutinized by Dr. Simmonds or a PRC PT/OT in raw format and interpretations will be recorded. Any ambiguity in the data will be adjudicated by an assessment sub-committee including the PI, the PT Interventionist(s), and Dr. Simmonds OR a PRC PT/OT. Data will be examined and discussed using unique identifiers only. Actiwatch data will be uploaded by a STRONG STAR IE at pre-treatment and all follow-up assessments and uploaded data will be scrutinized by the IE (who will be trained in the use of the Actiwatch system by the PI – with consultation from the manufacturer if needed) who will identify any aberrations in data that may require adjudication. Actiwatch data will be adjudicated using the same timeframe, methods, and subcommittee as the PT data.

NOTE: Actiwatch was chosen over Actical for this research based on data suggesting that actigraphy offers usable data after 10 days of wear time (Freedson, 2014; Mailey et al., 2014) and that wrist-worn actigraph is more sensitive to intensity of movement

than hip-worn actigraph (Mendoza et al., 2014). Thus, we will use the Actiwatch in 10-day epochs (participants will be asked to wear them for 12 or more hours per day; per Hermann et al., 2012) at every assessment period (instead of continuous wear for 6-months at a time). Previous studies have shown higher rates of adherence using 10-day epochs.

Medication Data will be adjudicated by the PI, the Research Coordinator, and Dr. Tabatha Blount (an expert in trauma and addiction comorbidity). Timeline followback interview and MQS-III data will be discussed for each participant by the IE and the Coordinator within two business days of each assessment. If there are any noted problems with the TLFB data, then the assessment will be adjudicated by the above sub-committee within 2 days of review. MEMS cap data will be gathered for each participant's reported "most helpful" pain medication and any opioid medications they are prescribed by VA or other providers outside the VA system during the course of the study. MEMS data will be downloaded for each participant at each assessment follow-up visit. Upon download, the IE will scrutinize downloaded data to ensure that it falls within an expected range. If aberrant or missing data are noted, these will be adjudicated with the above sub-committee (and potentially discussed with the manufacturer if hardware or software problems are suspected) in a deidentified format.

The primary opioid endpoint will be the timeline followback (TLFB) interview. The TLFB represents the primary measure of opioid use because of its reliability and sensitivity as a daily measure of opioid use and its lack of perceived stigma compared to regular urine tox screen. A trained and masked IE will administer TLFB asking participants about any opioid medication use and use of other medications for pain. The TLFB Interview for this study was adapted from Sobell and Sobell (1992) as a semi-structured clinical interview asking the participant to use a blank calendar to describe the number of pain pills taken each day for 30 days. Instructions are provided to help the interviewer guide the participant in completing the recall as accurately as possible. This method has been reliably used in other trials of medication/opioid use and abuse (Kunoe et al., 2009).

Study personnel blind to participant randomization can use the VA electronic health record (CPRS) to identify active and new opioid medication prescriptions from providers working in the VA system. Study physicians (Dr. Eapen and Dr. Jaramillo) get free access to the Prescription Access in Texas (PAT) prescription monitoring program to examine any and all Schedule II through V medications given by any provider in the State of Texas. Both CPRS and PAT (which maintains records of medications dispensed to a patient for 365 days) will be accessed at each Veteran's one-year follow-up visit to identify medications prescribed over the one-year study participation period.

Psychosocial Trauma and Emotional Measures will be adjudicated through the STRONG STAR Assessment Core using existing SOP for surveillance and adjudication of these measure. STRONG STAR has implemented this process for military and VA studies serving thousands of study participants across dozens of

studies (**see Appendix J**).

9.6 Data Analyses

Data Analysis: To examine our aims and hypotheses we will utilize the generalized linear model, which allows specification of an appropriate distribution for each outcome that can accommodate continuous outcomes (e.g., normal distribution with identity or log link for self-reported disability) and presence/absence outcomes (e.g, binomial with logit link for probability of daily opioid use). We will not stratify our analyses by PTSD or depression, but will account for these variables in our data analysis. Furthermore, we will attend to the influence of missing data on our analyses, and plan on conducting missing values analysis to inform several sensitivity analyses (e.g., LOCF, multiple imputation, etc.) to ensure an intent-to treat principle is observed. Specifically, we will examine the MAR assumption by examining patterns of missingness conditional on baseline assessments, treatment adherence, or other time-varying predictors. Our RCT has one primary endpoint (Oswestry), so both primary and secondary outcomes will be interpreted at a conventional level of statistical significance, $p < 0.05$. To adhere to NIH policy of examining gender and ethnic subgroup analyses, we will add interaction terms (i.e., treatment group x subgroup) for each of our planned analyses. Each analysis is further detailed below:

AIM 1: Assess the efficacy of the FORT-A Program for improved pain management outcomes in (N=130) polymorbid OEF/OIF/OND PRC Veterans with chronic orthopedic pain using a 1:1 randomized clinical trial comparing FORT-A to standard PRC care. To examine our primary hypothesis, we will compare the self-reported disability scores of the two groups at 12-month follow-up while controlling for baseline scores (i.e., an ANCOVA approach). A statistically significant main effect will be interpreted as the groups exhibiting differential change in regards disability. Secondary analyses will use growth curve modeling (mixed effects hierarchical regression with polynomial change parameters) which will model differences in change trajectory over time between the groups across assessment occasions.

AIM 2: Assess the efficacy of FORT-A for decreasing the rate of opioid medication recidivism compared to standard PRC care in a sample of OEF/OIF/OND polymorbid LBP Veterans. To examine our primary hypothesis, we will compare the rate of opioid medication recidivism between the two groups monthly from baseline to 12-month follow-up. As noted above, 30-40% of TAU participants are expected to meet criteria for opioid recidivism (use of any opioid medication for 3 days or more in the last 30 days at each assessment). A statistically significant main effect will be interpreted as the groups exhibiting differential change in regards disability. Secondary analyses will be conducted using growth curve modeling (i.e., mixed effects hierarchical regression with polynomial change parameters to model differences in the trajectory of opioid use over time between the groups by time).

EXPLORATORY AIM 3: To examine the role of helplessness and perceived burdensomeness in predicting the trajectory of change over time, we will use latent

growth curve modeling. We will first model the trajectory of change in the two primary outcomes as a function of group (Aim 1 and Aim 2). We will then model the trajectories of helplessness and perceived burdensomeness as a function of group. Assuming both associations are observed (i.e., that group status is related to changes in the outcomes and the mediators), we will conduct hierarchical entry of group status and each mediator to examine if group status is still associated with outcome after adjusting for changes in the mediators. This will allow us to assess the role of the mediators in predicting the outcome and the proportion of change trajectory attributed to changes in these mediators.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data will be collected by an Independent Evaluator blind to the randomized condition of the participant and entered into an online SQL database on the STRONG STAR server that is designed specifically for this study. As described in the STRONG STAR Data Entry SOP (see **Appendix S**), data are double-entered to minimize transcription errors and all data entry forms include appropriate data entry masks that limit the format and scope of entered data (to ensure that out-of-range values are not erroneously recorded) with provided feedback if entered data exceed expected ranges. STRONG STAR has developed strict rules guiding the translation of assessment measures and data recording forms into digital formats as outlined in **Appendix T**. Paper copies of assessments are also uploaded and tagged to the assessment record for review by the IEs or other study staff if adjudication of responses is needed. The STRONG STAR Network is FISMA compliant and has received permission from the VHA for the storage of Veteran study data (which is very strictly controlled by the VA system). Because the STRONG STAR Database is accessible through a secure internet portal, data can be entered into the system directly from any VA computer with internet access (of which this study currently has dedicated access to two through the PRC). To ensure confidentiality of patient records, all data are entered into study records using the participant's unique ID. A link between identifiers and the ID is maintained in a separate data table with access restricted to individuals who are not blind to patient identifiers (e.g., study Coordinator, interventionists).

10.2 Data Management

Data will be coded using an assigned number. Data collected during treatment will be entered into a secure STRONG STAR database, and hardcopies will be placed into a lock box which will be transported by car to University of Texas Health Science Center San Antonio (UTHSCSA) STRONG STAR offices by a STRONG STAR staff member who will place it into the locked cabinets at the STRONG STAR offices. Audio and video recordings will be uploaded to a secure STRONG STAR server over an encrypted network connection between VA networks and UTHSCSA networks. Members of the study team will have access to the data. Every member of the Research Team will be trained and monitored about how to handle and protect both medical and research records. Furthermore, the Research Team strictly controls access to study data using policies and procedures developed specifically for the

STRONG STAR Research Consortium. Adverse Events will be immediately brought to the study PI and reported to the IRB and funding agency. AE's will be identified by unique identifier to protect blinding of the PI. If the participant's identity is needed to effectively manage an AE, then the Study Coordinator will link the unique identifier to the specific participant (the Coordinator will maintain a link between PHI and unique identifiers through the STRONG STAR Data Core dashboard). A STRONG STAR Data Safety and Monitoring Plan (DSMP) has been developed in accordance with the National Institutes of Health (NIH) Office of Human Research Protection (OHRP) to assure the appropriate clinical safety monitoring of study subjects participating in all of its studies. The STRONG STAR database has been certified as FISMA-compliant and has been formally cleared for the management of Veteran data through the VA.

10.3 Quality Assurance

10.3.1 Training

Sections 5.1, 5.2, and 5.4 of this protocol describe various components of training for assessment and intervention for this study. STRONG STAR uses circumscribed certification processes for assessment and intervention to ensure that individuals completing assessment and intervention are trained to an acceptable standard and that resulting assessment and intervention is of sufficient quality to provide and sensitively assess systematic treatment effect to the greatest extent possible.

10.3.2 Quality Control Committee

A STRONG STAR Research Assistant outside of this study will be asked to complete a quarterly External Protocol Monitoring Checklist (**Appendix U**) for submission to the Study Coordinator, PI, and the STRONG STAR Admin Core for review. Discrepancies or problems will be addressed by the Admin Core and the PI acting as the quality control committee.

10.3.3 Metrics

As shown in **Appendix U**, quality control metrics include appropriate organization of study documents, confirmation of regulatory document versions, verification of enrollment protocols, documentation and adjudication of AEs, storage of data, and documentation/report/adjudication of protocol deviations.

10.3.4 Protocol Deviations

The STRONG STAR Protocol Deviation and AE SOP (**Appendix V and W**) thoroughly describes the mechanisms and responsibilities for tracking, documenting, and adjudicating protocol deviations. Briefly, each participant chart will include a Protocol Variance and Deviation Log that will be used to track and document deviations from protocol. Responsibility for tracking deviations lies with the study staff member who first discovers a provider or participant deviation from protocol (advertent or inadvertent). STRONG STAR Regulatory (aka the STRONG STAR Admin Core) is responsible for working with the PI and the Coordinator to assess the nature of the deviation and the adjudication of the deviation. Deviations are entered

in the STRONG STAR Database, reported to the IRB (the SOP describes the BAMC IRB, but this protocol will report to the UTHSCSA and VA IRBs), and included in annual reports to the funder.

10.3.5 Monitoring

Monitoring of study data and protocol deviations is described in **Appendix V** and as outlined in the Data Safety Monitoring Plan (DSMP) for this study. The Study Coordinator is responsible for updating the STRONG STAR Regulatory Coordinator about all protocol deviations. The Regulatory Coordinator will ensure that the IRB, PI, and funder are aware of deviations through regular reporting mechanisms (e.g., Progress Reports, Progress Reviews, ad hoc meetings) and the PI is ultimately responsible for all reporting. The Study Coordinator will review all study charts within 3 business days of assessment and once a week during intervention phase to identify any noted deviations (notated in the chart by the study personnel responsible for the deviation as described in **Appendices V and W**).

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (**Appendix D**) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The consent form should be separate from the protocol document. Regulatory review will occur through the UTHSCSA/VA IRB (of which the PI currently serves as the Alternate Chair) and the VA R&D Committee (see **Appendix X**).

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g. person with power of attorney), this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record.

11.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet at the VA PRC. Data will be entered into the secure STRONG STAR Database from the VA. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NCCIH, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the

FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12. COMMITTEES

STRONGSTAR Administrative Core – The STRONGSTAR Administrative Core provides administrative support and oversight for all STRONGSTAR and STRONGSTAR affiliated studies. Support functions include: assistance of recruitment and hiring for study personnel, assistance with regulatory and compliance paperwork and procedures (e.g., IRB, annual progress reviews), VA and DoD integration (e.g., securing and maintaining research infrastructure in VA and DoD facilities). The Administrative Core will arrange a kick-off meeting including all study personnel (overseen by the study PI) during which all logistical issues for this research will be discussed and finalized (see **Appendix Y**). A summary of the kick-off meeting will be submitted to the funder during quarterly progress reports.

STRONGSTAR Biostatistics, Data, and Computing Services Core (BDCS Core) – The STRONGSTAR BDCS Core oversees the input, storage, and output infrastructure and policies for all STRONGSTAR and affiliate study data. BDCS works with the PI to develop a customized SQL database with a secure online portal capable of maintaining VA data (based on a standing agreement between the VA and STRONGSTAR; storing VA data offsite ***must*** be approved by the VA). https://delta.uthscsa.edu/strongstar/cores.asp?c=3

STRONGSTAR PI Committee – The STRONG STAR Principal Investigators Committee is responsible for overseeing who each STRONG STAR and affiliated study fits into the local (i.e., STVHCS) research landscape and how data are disseminated. The PI Committee helps explore how a study may intersect of overlap with other STRONG STAR studies and helps troubleshoot how a study can recruit and intervene in light of other research activities in the geographic area. Additionally, the PI Committee has established guidelines describing how decisions should be made if a participant seeks involvement in more than one STRONG STAR study (see **Appendix Z**).

Opioid Safety Initiative Committee – The OSI Committee plans and implements OSI efforts in the STVHCS (see 5.3.4).

13. PUBLICATION OF RESEARCH FINDINGS

All STRONG STAR and STRONG STAR affiliated studies must request and approve publication and/or presentation of research findings through the STRONG STAR Principal Investigators Committee (see **Appendix ZZ**). Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

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15. SUPPLEMENTS/APPENDICES (SOP = "Standard Operating Procedure")

Appendix	**Contents**
-- *none* --	Data Safety Monitoring Plan (DSMP)
A1	Consent to contact form
A2	IRB-approved consent form
A3	NCCIH Screening Log
A4	SOP – Unique ID assignment
B	FORT-A manual
C	Manual of Procedures for PT, individual psychotherapy, team staffings (still under development)
D	OSI information
E	Attendance form
F	Adherence assessment
H	Screening call sheet (I accidently skipped G! There is no Appendix G)
I	Data entry SOP

J	Adverse events monitoring SOP
K	Medical record documentation SOP
L	Adverse events documentation SOP
M	Adverse events adjudication SOP
N	PCL scoring guidelines
O	ASAP session SOP
P	Suicide risk monitoring and management SOP
Q	External safety monitoring protocols
R1	Referral resources
R2	Referral tracking form
R3	Distance assessment SOP
S	Data entry and access SOP
T	Instrument review SOP
U	External monitoring checklist
V	Data safety monitoring plan
W	Protocol deviation SOP
X	Regulatory policies and procedures
Y	Kick off meetings
Z	Multiple study enrollment policy
ZZ	Publication SOP