

Proof of Concept Study to Treat Negative Affect in Chronic Low Back Pain

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Proof of Concept Study to Treat Negative Affect in Chronic Low Back Pain

Study Description: Chronic low back pain patients (CLBP) often suffer from coexisting psychiatric and psychological symptoms of depression, anxiety, fear avoidance, and/or high levels of pain catastrophizing. These symptoms can be grouped together as negative affect (NA). High levels of NA is associated with poor pain treatment outcomes such as higher levels of pain, impairment of function, opioid misuse, and likelihood to be prescribed more opioids. As such, patients with chronic low back pain and high NA have the worst treatment outcomes and are most treatment-resistant. While effective treatments exist to improve NA, which then improves pain and function, not every patient responds. We have little understanding of the psychological, behavioral, and physiological mechanisms by which improving NA leads to improved pain and function, or conversely, why these treatments fail. Thus, it is crucial to underscore the importance of NA as a treatment target and the necessity to address the unmet need for better comprehensive pain care in CLBP patients with high NA. An improved understanding and improvement in the development of better multimodal treatments will lead to better treatments for high chronic pain patients, particularly in those with chronic pain and high NA.

This randomized trial study will include the prevalent subgroup of patients with CLBP who have high NA and may or may not be taking opioids prescribed for pain. We will determine if single treatment, antidepressants (AD) or fear avoidance rehabilitation (EFAR), vs. the combination of the two is the better treatment for CLBP patients with high NA.

Objectives:

Primary To compare the effectiveness of combination therapy with AD+EFAR vs. each treatment alone to improve pain, self-reported function, depression, and anxiety in patients with chronic low back pain and high negative affect.

Secondary To identify predictors of treatment responses.

Exploratory To obtain qualitative feedback from participants that will inform the development of an intervention to reduce the impact of stigma

Endpoints: PRIMARY ENDPOINT: *Hypothesis 1:* AD+EFAR will show the most improvement in pain, function, and depression compared to single treatment with AD or EFAR alone, with opioid use moderating a less robust response to any treatment.

The primary outcome is a composite response measure of changes in pain, function, and depression. There are two sub-component measures: the

rate of pain+ function responders and the rate of depression responders in each group. A participant could be a pain+function responder, a depression responder, both, or neither.

SECONDARY ENDPOINT: *Hypothesis 2*: AD+EFAR will be the most effective in preventing opioid misuse and will be associated with greater reductions in daily opioid dose vs. AD or EFAR alone.

Secondary outcomes include changes in opioid misuse, opioid dose, sleep, anxiety, pain interference, and a variety of patient reported outcomes.

EXPLORATORY ENDPOINT: Qualitative feedback obtained in two qualitative interviews, one prior to the start of treatment and one following the first phase of treatment, for an analysis of stigma-related issues.

Study Population:

Sample size: up to 330, if needed, related to the rate of dropouts

Gender: Male/Female

Age: 18-75

Health status: Diagnosed with chronic low back pain who may or may not be on opioids

Study Site Locations: Pittsburgh, Boston, Rochester

Phase:

2

**Description of
Sites/Facilities Enrolling
Participants:**

There are a total of 3 study site locations (US sites):

- **University of Pittsburgh** – The clinical visits will take place at the UPMC Centre Commons site, which is the largest of pain medicine clinics within UPMC and is experienced in managing pain. This is the research office location of the leading PI, Dr. Wasan, and has facilities for research visits and the research assistants. Several other University of Pittsburgh and UPMC clinical pain research studies have been conducted at this site. In addition, recent prior cross-sectional and longitudinal studies of back pain patients conducted at Centre Commons by Dr. Wasan as a PI or co-investigator have managed to recruit hundreds of participants.
- **Brigham and Women's Hospital** – In Boston, the Center for Arthritis and Joint Diseases at Brigham and Women's Hospital is one of the busiest practices in the country, providing care for over 25,000 patients with arthritis and its allied conditions, such as CLBP, on an annual basis. Many patients with back pain and other musculoskeletal pain conditions are seen at the BWH Pain Management Center, where Dr. Edwards is on staff. Participants are identified through clinic referrals, flyers, and community ads, and use of the Research Patient Data Registry (RPDR), a centralized clinical data warehouse that provides access to millions of patient records (see: <http://rc.partners.org/rpdr>).
- **Mayo Clinic** – At the Mayo site, their primary recruitment strategy will be through the Pain Clinic and the Spine Center. These two clinics have treated 12,000 patients with chronic low back pain in the past 12 months. In addition, Dr. Hooten have conducted several chronic pain treatment studies of similar duration as this proposed

**Description of Study
Intervention:**

study, with an overall retention rate of 85%. In our preliminary data, the compliance with taking ADs or attending all EFAR sessions has been over 70%, with subject retention rates of 85% at 4 months. All 3 sites have previously recruited CLBP patients for trials and have the resources to conduct this study.

This study will include the prevalent subgroup of patients with CLBP who have high NA and may or may not be taking opioids prescribed for pain. We will determine if antidepressants (AD), fear avoidance rehabilitation (EFAR), or the combination of the two is the better treatment for CLBP patients with high NA. The study intervention will involve 3 treatment arms and are detailed as follows:

- **Antidepressant** – The study intervention for Antidepressant treatment implements the use of AD medication to observe pain, function, and depression outcomes. Participants will be prescribed antidepressants during Study Visit 2 and will follow the guidelines provided. A modified version of the antidepressant treatment protocol from the SCAMP trial will be used. The Antidepressant Treatment History Form will be completed by participants during Study Visit 1 or 2 to assess adequacy of any prior antidepressant medication treatment. Participants who are not taking an antidepressant at study entry will start at Step 1 detailed in the Medication Table. Participants who are currently prescribed an AD will be assessed regarding if the current AD or augmentation agent is subtherapeutic and dosed inadequately. Procedures involving AD visits, AD prescribing, and collection of AD-related assessments will be administered by the nurse practitioner or psychiatrist. See **Section 8.2, Treatment Arm 1: Antidepressant (AD)** in the MOP.
- **Enhanced Fear Avoidance Rehabilitation (EFAR)** – The study intervention for EFAR treatment involves the use of physical/occupational therapy and pain education in order to potentially improve pain, function, and depression outcomes. The participant will be provided verbal and written educational material by the physical/occupational therapist during their EFAR session. An EFAR session consists of pain education and engagement in gradual exposure to activities participants are apprehensive about. EFAR treatment for EFAR treatment arm will start at Week 2 depending on participant's availability
- **AD+EFAR** – The study intervention for AD+EFAR treatment involves the combination of antidepressant medication and EFAR sessions. Subjects will receive both antidepressants and EFAR treatment simultaneously as compared to the individual treatments. AD treatment will start in Week 2 and EFAR treatment for AD+EFAR treatment arm will start at Week 4 or 5 depending on the participant's availability.

Study Duration:

42 months; 3.5 years from when the study opens to enrollment until completion of data analyses

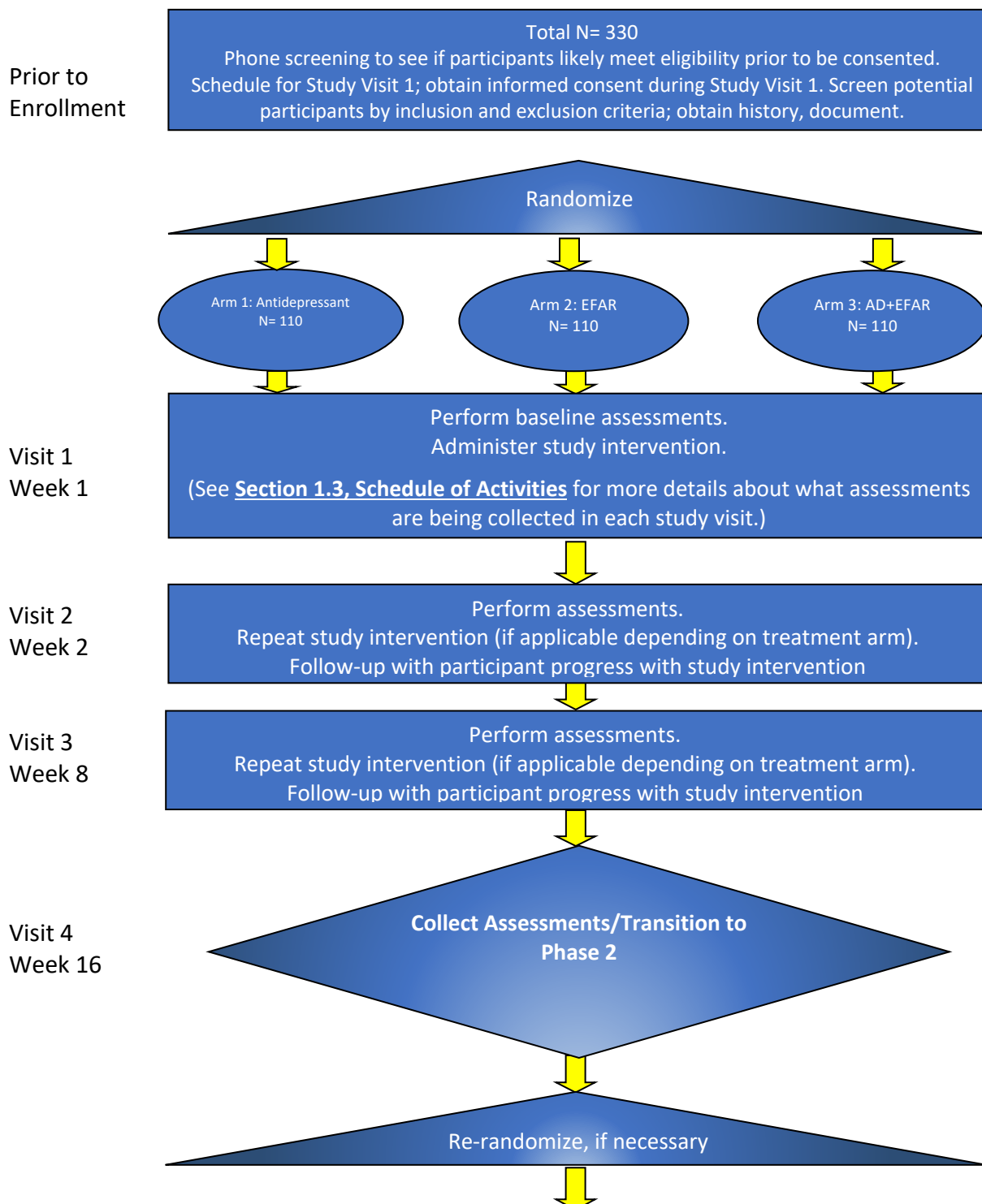
Participant Duration:

8 months (32 weeks + 5 days* due to gap from when subjects receive AD medication)

*Week 2 will be treated as a 12-day week.

1.2 SCHEMA

Study Flow diagram



Weeks 17-32

Collect biweekly online surveys
Follow-up with participant's progress on home program

1.3 SCHEDULE

Procedures	Phone Screening	Enrollment/Baseline Visit 1, Day 1	Qualitative Interview 1 Day 1±7 Days	Study Visit 2 Day 28±7 days	Study Visit 3 Day 56 ±7 days	Final Study Visit 4 Day 112 or Week 16	Qualitative Interview 2 Day 112 ± 14 Days	EFAR Visit Week 2 or 4 8 weekly sessions	Weekly Surveys Week 1-16 (Week 17-32 bi-weekly)
Informed consent		X							
Demographics		X							
Medical history		X							
Randomization		X							
Qualitative Interview			X				X		
AD medication prescribing				X					
Administer Conditioned Pain Modulation (CPM)				X	X	X			
Urine Drug Toxicology		X			X	X			
Urine Pregnancy		X							
Antidepressant Treatment History Form (completed at Visit 1 or 2)		X		or X					
Self-Administered Co-Morbidity Questionnaire		X							
BACPAC Minimum Dataset		X			X	X			
Addiction Behavior Checklist (ABC)		X			X	X			
Drug Misuse Index		X			X	X			
Current Opioid Misuse Measure (COMM)		X			X	X			
Opioid Side Effect Checklist		X		X	X	X			
Opioid Craving Questions		X		X	X	X			I
Medication Log/Pain Self-management Log		X		X	X	X			I (pain self-management log)
Complete Case Report Forms (CRFs)		X		X	X	X			
Widespread Pain Index (WPI) + Symptom Severity		X		X	X	X			
PainDETECT		X		X	X	X			
PROMIS-2 Item Cognitive Screener (PROPr)		X		X	X	X			I
PROMIS Pain Behavior		X		X	X	X			
Fear Avoidance Beliefs Questionnaire—physical activity items (FABQ-PA)		X		X	X	X			
Pain Catastrophizing Scale		X		X	X	X			
Columbia-Suicide Severity Rating Scale (CSSRS)				X	X	X			
Pre-Treatment Assessment Form				X	X	X			
Treatment Helpfulness Questionnaire				X	X	X			
Patient Global Impression of Change (PGIC)					X	X			
PHQ-4	X	X							
FIBSER									I (every other week starting week 3)
AD Side Effects Checklist									I (every other week starting week 3)
Fear of Daily Activities Questionnaire (FDAQ)								X	
Adverse event review and evaluation				X-----X				X	
Study Completion of Phase 1						X			

Yellow: Opioid-users **Blue:** Participants receiving AD **Green:** Participants receiving EFAR **Pink:** Participants in qualitative substudy

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic low back pain patients often suffer from coexisting psychiatric and psychological symptoms of depression, anxiety, fear avoidance, and/or high levels of pain catastrophizing. These symptoms can be grouped together as negative affect (NA). High levels of NA is associated with poor pain treatment outcomes such as higher levels of pain, impairment of function, opioid misuse, and likelihood to be prescribed more opioids. [3, 5, 31-37] As such, patients with chronic low back pain and high NA have the worst treatment outcomes and are most treatment-resistant. Moreover, despite multiple randomized controlled trials indicating that improving NA improves low back pain,[10, 12, 82] treating the affective component of pain is not commonly viewed as an analgesic mechanism, but instead as a modality to help patients better cope with pain or reduce their suffering. Due to this gap, current multimodal treatments specifically designed to target chronic pain are not always effective and suggests that finding the right combination of treatments and target group are crucial.[71-73] We have little understanding of the psychological, behavioral, and physiological mechanisms by which improving NA leads to improved pain and function, or conversely, why these treatments fail. Thus, it is crucial to underscore the importance of NA as a treatment target and the necessity to address the unmet need for better comprehensive pain care in CLBP patients with high NA. The proposed study is unique in targeting the multidimensional aspects of negative affect, e.g., depression, anxiety, and fear avoidance. In doing so, this can lead to more effective pain treatments within clinical care for CLBP patients, particularly in those with chronic pain and high NA.

Intersectional health-related stigma (IHRS) occurs when multiple health conditions converge (46). Studies examining IHRS in the context of other chronic health conditions, especially HIV (46-48), suggest that intersectional stigma is associated with worse health behaviors and outcomes including poor medication adherence and increased depression (46, 48-50). Due to high rates of comorbidity among chronic pain, depression, and opioid use (51), patients with CLBP may identify with multiple marginalized groups. However, there are no studies to date that examine the intersectionality of stigma related to mental health, chronic pain, and opioid use and how such intersectional stigma influences treatment outcomes.

This study will include the prevalent subgroup of patients with CLBP who have high NA and may or may not be taking opioids prescribed for pain. We will determine if antidepressants (AD), fear avoidance rehabilitation (EFAR), or the combination of the two is the better treatment for CLBP patients with high NA. This study will also identify which patients are most likely to respond to components of the intervention. We are proposing a clinical model hypothesizing that: (1) AD+EFAR will show the most improvement in pain, function, and depression compared to AD or EFAR alone, with opioid use moderating a less robust response to any treatment. (2) AD+EFAR will be the most effective in preventing opioid misuse and will be associated with greater reductions in daily opioid dose vs. AD or EFAR alone. (3) Higher depression subjects will respond best to ADs and worse functioning subjects to EFAR. (4) Improvements in conditioned pain modulation (CPM) will precede to improvements in pain

and mediate treatment responses. (5) Higher levels of IHRS prior to treatment will be associated with poorer treatment outcomes across all treatment conditions. (6) Higher levels of IHRS prior to treatment will be associated with poorer treatment outcomes across all treatment conditions.

2.2 BACKGROUND

Chronic Pain and Negative Affect

CLBP affects an estimated 50 million U.S. adults.[15] Negative affective disorders afflict 40% of CLBP clinic populations (~10-20 million) and is most often major depression with anxious features,[1] along with a range of pain-related psychological symptoms, such as elevated fear-avoidance behaviors and pain catastrophizing.[2] These conditions, despite their distinct features, may be grouped, since they are highly co-morbid in patients with chronic pain, and they have cross correlations of .6-.80.[21] This suggests an underlying construct, known as Negative Affect (NA).[2, 22-27] This conceptual approach is supported by the NIMH Research Domain Criteria initiative (RDoC), which identifies 'Negative Affect' (i.e., the Negative Valence domain) as a designated priority for trans-diagnostic treatment interventions.[28-30]

High NA magnifies pain and impairs function, leading to poor pain treatment responses, more prescribing of opioids, and more opioid misuse vs. in those with low NA.[1, 3-7] To achieve the mission of the Federal Pain Research Strategy,[8] address the opioid crisis, and improve outcomes in CLBP patients with high NA, improved multimodal pain treatments are essential. A crucial deficit in the treatment of NA in CLBP (which is often only antidepressants) is the lack of focus on the behavioral inactivation related to high NA (i.e., poor function and inactivity).[9] We conducted separate controlled trials showing that treating high NA in CLBP with antidepressants (AD) or fear avoidance-based physical therapy improves pain, function, and NA by 25-40% each.[10-12] To improve the physical therapy, we then added pain education and motivational messaging on a mobile app into an 8-session protocol delivered by physical or occupational therapists (Enhanced Fear Avoidance Rehabilitation-EFAR). We found it more effective than usual care. A key next step is to determine the most effective treatment for CLBP with high NA (AD, EFAR, or AD+EFAR) and secondly, to identify which patients are most likely to respond to components of the intervention. Using NA as the clinical and mechanistic target, we will test a multimodal intervention to treat NA and CLBP together in a randomized trial of antidepressants (AD) vs. rehabilitation (EFAR) vs. AD+EFAR. We will include detailed phenotyping and an adaptive design to better identify responders and non-responders to each intervention. These approaches are necessary for a subgroup who have an otherwise treatment refractory condition with high pain and disability (known as high impact chronic pain).[13] Our central hypothesis is that a combined biological and behavioral activation approach (AD+EFAR) is most effective.

Opioid Misuse and Negative Affect

Surveys have shown that 52% of 1,860 CLBP patients from across the USA were prescribed opioids.[41] While opioid prescribing has decreased,[42] the subgroup with high NA is prescribed opioids at greater rates, due in part, to lack of improvement.[43-46] The latest data indicates that 51% of all opioids are prescribed to patients with pain and depression or anxiety disorders.[47, 48] High NA in CLBP is also associated with greater opioid misuse,[49] with rates ranging from 40-60%.[4, 50, 51] In this proposal and in our prior studies, we use the FDA definition of prescription opioid misuse, "the taking of medication with a therapeutic intent in a manner other than as prescribed,"[52, 53] which includes using opioids at higher doses or frequency to improve pain, mood, or sleep. We have found that such self-medication of anxiety and depression symptoms is common in CLBP patients with high NA.[54]

Prescription opioid misuse is considered a mild opioid use disorder by DSM-5 criteria,[55, 56] and we published a recent review demonstrating that “opioid misuse” maps onto a mild opioid use disorder diagnosis.[57] Opioid misuse can lead to opioid abuse, dependence, or addiction (moderate or severe opioid use disorders).[51, 58, 59] Meta-analyses find that 5-15% of chronic non-cancer pain patients prescribed opioids will develop an opioid addiction,[60] and prescription opioid use disorders are at epidemic levels in the US.[61, 62]

Patients with chronic pain and high NA are also more likely to be prescribed higher opioid doses (likely due to poor analgesia), which places them at a greater risk of inadvertent overdose and death (either unintentional or intentional by suicide).[59, 61, 63] Indeed, a recent review in the New England Journal of Medicine concluded that patients with chronic pain and comorbid depression who are prescribed opioids are in one of the highest risk categories for suicide.[64] Notably, we found whereas pain level was not a predictor of prescription opioid misuse,[65, 66] high NA was the most prevalent and powerful risk factor.[50, 67] This suggests that targeting NA is likely the most effective pathway to preventing opioid misuse.[68] As such, this recent NEJM review highlighted the need for better combined treatment of chronic pain and depression in medical settings specifically.[64] The 2016 CDC guidelines for opioid prescribing for chronic pain also conclude that patients with high NA are more likely to be prescribed opioids, and have worse treatment outcomes and poorer analgesia.[69] The National Academy of Medicine has also declared that decreasing prescription opioid misuse is a public health priority.[70]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Common risks

- **Antidepressant: Aripiprazole** – difficulty with speaking, loss of balance control, stiff muscles, restlessness, uncontrolled movements, nausea, vomiting, anxiety, constipation, dizziness, headache
- **Antidepressant Medication: Bupropion** – Loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, insomnia, muscle pain, nausea, fast heartbeat, urinating more often
- **Antidepressant Medication: Duloxetine** – Dry mouth, drowsiness, tired feeling, mild nausea, loss of appetite, constipation
- **Antidepressant Medication: Escitalopram** – Nausea, sleepiness, weakness, dizziness, feeling anxious, trouble sleeping, sexual problems, sweating, shaking, not feeling hungry, dry mouth, constipation, diarrhea, weight gain or weight loss
- **Antidepressant Medication: Mirtazapine** – Sleepiness, increased appetite, weight gain, dry mouth, constipation, dizziness, abnormal dreams
- **Antidepressant Medication: Sertraline** – Nausea, loss of appetite, diarrhea, insomnia, sleepiness, sexual problems, tremor or shaking, fatigue, agitation, weight gain or loss
- **Antidepressant Medication: Venlafaxine** – Drowsiness, dizziness, feeling nervous, strange dreams, increased sweating, blurred vision, dry mouth, changes in appetite or weight, mild nausea or constipation
- **Antidepressant Medication: Nortriptyline** - Suicidal thoughts or actions, sudden changes in mood, behaviors, thoughts, or feelings, nausea, drowsiness, weakness, tiredness, excitement, anxiety, nightmares, dry mouth, changes in appetite or weight, constipation.

- **Antidepressant Medication:** St John's Wort - Stomach upset, hives or other skin rashes, fatigue, restlessness, headache, dry mouth, diarrhea, and feelings of dizziness or mental confusion
- **Conditioned Pain Modulation** – Temporary discomfort
- **Graded Exposure Physical Therapy** – Anxiety, temporary discomfort during treatment sessions
- **Opioid-Weaning Procedures** – Psychological withdrawal, Increased pain

Infrequent risks

- **Antidepressant: Aripiprazole** – Blurred vision, fever, fast or slow heartbeat, trouble breathing or swallowing, high or low blood pressure, agitation, seizures
- **Antidepressant Medication: Bupropion** – Suicidal thoughts or actions, seizures, high blood pressure, manic episodes (having greatly increased energy, racing thoughts, reckless behavior, severe trouble sleeping)
- **Antidepressant Medication: Duloxetine** – Nausea, stomach pain, itching, loss of appetite, dark urine, clay-colored stools, jaundice (yellowing of the skin or eyes), light-headedness, agitation, hallucinations, fever, fast heart rate, overactive reflexes, vomiting, diarrhea, loss of coordination, stiff muscles, high fever, sweating, confusion, tremors, easy bruising, unusual bleeding, painful or difficult urination, headache, trouble concentrating, memory problems, weakness, feeling unsteady, seizure, short breathing, severe skin reaction fever, sore throat, swelling in your face or tongue, eye irritation, skin pain, skin rash that spreads (especially in the face or upper body) and causes blistering and peeling
- **Antidepressant Medication: Escitalopram** – Suicidal thoughts or actions, changes in the electrical activity of your heart (QT prolongation), Serotonin Syndrome (agitation, hallucinations, coma, twitching, racing heart, sweating, fever, muscle rigidity), abnormal bleeding, seizures, manic episodes (having greatly increased energy, racing thoughts, reckless behavior, severe trouble sleeping), low salt levels in the blood
- **Antidepressant Medication: Mirtazapine** – Suicidal thoughts or actions, Serotonin Syndrome (agitation, hallucinations, coma, twitching, racing heart, sweating, fever, muscle rigidity), decreased white blood cell count, seizures, manic episodes (having greatly increased energy, racing thoughts, reckless behavior, severe trouble sleeping), low salt levels in the blood, increased cholesterol and triglyceride levels
- **Antidepressant Medication: Sertraline** – Suicidal thoughts or actions, changes in the electrical activity of your heart (QT prolongation), Serotonin Syndrome (agitation, hallucinations, coma, twitching, racing heart, sweating, fever, muscle rigidity), abnormal bleeding, seizures, manic episodes (having greatly increased energy, racing thoughts, reckless behavior, severe trouble sleeping), low salt levels in the blood
- **Antidepressant Medication: Venlafaxine** – Seizure (convulsions), stiff muscles, high fever, sweating, confusion, fast or uneven heartbeats, tremors, light-headedness, agitation, hallucinations, fever, fast heart rate, overactive reflexes, nausea, vomiting, diarrhea, loss of coordination, headache, trouble concentrating, memory problems, weakness, feeling unsteady, confusion, hallucinations, fainting, short breathing, cough, chest tightness, trouble breathing, easy bruising
- **Antidepressant Medication: Nortriptyline** - Jaw, neck, and back muscle spasms, slow or difficult speech, shuffling walk, uncontrollable shaking of a part of the body, fever, difficulty breathing or swallowing, rash, yellowing of the skin or eyes, irregular heartbeat.
- **Antidepressant Medication:** St John's Wort - Increased sensitivity to sunlight (photosensitivity/ photodermatitis)

- **Breach of Confidentiality** – There is a potential risk of breach of confidentiality that is inherent in all research protocols. There is a possibility that if research data were to become known, this knowledge could potentially impact a subject's future or have a negative impact on family or social relationships. With the use of SMS messaging, there is a potential risk that messages could be intercepted by a third party. For subjects who are opioid users, some of the text messages indicate that the subject is taking opioid medication, and this could have a negative impact on the subject's life.
- **Opioid-Weaning Procedures** – Restlessness, lacrimation (watery eyes), rhinorrhea (runny nose), yawning, perspiration (sweating), chills, myalgia (muscle pain), mydriasis (dilated pupils), irritability, anxiety (nervousness), backache, joint pain, weakness, abdominal cramps, insomnia (trouble sleeping), nausea (upset stomach), anorexia (decreased appetite), vomiting, diarrhea, increased blood pressure, increased heart beat, faster breathing

2.3.2 KNOWN POTENTIAL BENEFITS

Immediate potential benefits:

- Improvement in average daily pain and function
- Reduction in depression symptoms

Drs. Bair and Kroenke's 12-month randomized controlled trial, Stepped Care for Affective Disorders in Musculoskeletal Pain (SCAMP), tested AD and pain self-management education in sequential order vs. usual care. SCAMP enrolled 250 patients either on or off opioids, with CLBP or knee pain and high NA.^{10, 88, 89} Antidepressants were the first 3 months followed by 3 months of pain self-management delivered by nurse care managers. At 6 months, 47% of the 123 intervention subjects had at least 30% improvement in average daily pain and function,⁸⁵ or at least 50% improvement in depression symptoms. There were 29% who were combined pain, function, and depression responders, vs. 10% in the usual care group. This response was sustained at 1 year.

Additionally, randomized trials of 6 months duration by Dr. Steve George have shown the effectiveness of 2 months of fear avoidance-based PT vs. usual care in reducing NA and pain in low back pain patients on or off opioids.^{12, 90} These two RCTs enrolled 174 patients and had an average 70% treatment completion and study retention rate at six months. The 67 patients receiving FABPT had an average 59% improvement in pain, 40% improvement in fear avoidance beliefs, and 58% improvement in self-reported function vs. smaller changes with usual care ($p < .05$). These studies and others have demonstrated that the improvements in pain reported after FABPT are mediated by decreasing NA.^{91, 84}

Long-range potential benefits:

- Improvement in pain and function
- Reduction in depression, anxiety, or other pain-related psychological symptoms
- Improvement in overall mood

Although the benefits and responses were sustained at 1 year in the SCAMP trial, it is possible that some of the participants will derive direct long-term benefit from participation in the study, such as improvements in pain, function, and mood. Participants who wish to continue their treatments at the conclusion of the study will be given the opportunity to do so at UPMC Centre Commons Pain Clinic, Brigham and Women's Hospital, or Mayo Clinic.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Antidepressant Intolerance

We are following a well-established antidepressant medication protocol based off of SCAMP trial, and these events were exceedingly rare during this study. Side effects of the antidepressant medications are monitored at AD Visits with the nurse practitioner. The visit will allow the nurse practitioner to adjust the medication after discussion with participant, if needed. Nausea, sedation, and agitation can frequently occur with medication titration. The patient will be reassured of the likely temporary nature of these symptoms. We also have the option of switching out of antidepressants if needed. Since we are using 2 modalities to improve negative affect, if a subject cannot tolerate antidepressants at all, they can still continue with PT treatments. Our hypotheses study the relationships between negative affect and treatment responses. While it is ideal, it is not necessary that both treatment types are adhered to by every subject.

Severe Psychiatric Symptoms

Due to the nature of the study, the population pool is made up of those with high negative affect and chronic low back pain. As a result, participants may suffer from depression, anxiety, and/or other pain-related psychological symptoms upon enrollment. The participant's psychiatric symptoms are continually reevaluated during the study (e.g. nurse practitioner assesses participant suicidal behavior with CSSRS survey). All study physicians and nurse practitioners are suitably trained to take the necessary steps if symptoms significantly worsen, including emergency department referral and involuntary assessment as necessary.

Breach of Confidentiality

No identifying information is written on the screening script, and the script is destroyed after the phone call after ascertaining that the subject is not eligible for or declines participation in the research study. Scripts that will be retained will be kept in a secure, locked file cabinet. Data will be entered into password secured databases by staff authorized by the principal investigator to do this, and they will abide by confidentiality regulations of the IRB. These data are password secured for minimal access to authorized personnel associated with the study. No research documents will contain the names of participating subjects. Subject anonymity will be preserved by the use of a code number. No subject will be identified by any published report. Rating scales will be performed by trained and experienced research personnel.

Physical Therapy

Graded exposure PT or OT can temporarily aggravate pain during treatment sessions, and teaching the patient to tolerate this discomfort is part of the therapeutic process to overcome fear of pain and movement. The PT/OT therapists are well-trained in this and will evaluate the Fear of Daily Questionnaire at the beginning of each EFAR session to introduce activities and degree of exposure gradually.

Opioid Weaning

At week 4, a study physician will suggest to each subject that over the next 4 weeks they voluntarily reduce their daily opioid dose by approximately 15%, and prescriptions will reflect this change. This slow and shared decision-making process is suggested by the CDC, and will be repeated at each of the next 3 monthly visits, as tolerated. Weaning is done slowly according to a shared decision between participant and study physician. This is done as tolerated by the study subjects. Subjects can wean faster and come off opioids altogether if requested. While withdrawal symptoms may arise and are uncomfortable, they

are not dangerous and participants can always choose to stop the weaning at any time and still remain in the study. Weekly RedCap assessments completed by participants will record the opioid side effects and subjects' opioid intake. Study physicians will also check-up on participants and their opioid-weaning progress every month, starting Week 4. This will allow the physician to adjust their opioid prescription, as needed.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
<i>To determine if single treatment with antidepressants (AD) or fear avoidance rehabilitation (EFAR), vs. the combination of the two is the better treatment for chronic low back pain patients with high negative affect.</i>	<ul style="list-style-type: none"> • Composite response metric of changes in pain, function, and depression • Combined response metric of pain+function changes • Changes in depression symptoms 	<ul style="list-style-type: none"> • Core outcome domains for pain clinical trials. • Depression is a primary treatment target of the intervention
Secondary		
To identify predictors of treatment responses.	<i>Strength of predictors in a logistic regression model</i>	<i>Necessary for phenotype-treatment matching in the future</i>
Opioid misuse	<i>Opioid misuse rates between groups</i>	<i>Important possible downstream effect of the intervention</i>
Tertiary/Exploratory		
<i>Conditioned pain modulation</i>	<i>CPM changes over the course of treatment</i>	<i>Measure of change in endogenous analgesic systems</i>
<i>To examine IHRS as a potential treatment moderator</i>	<i>Moderating effects of IHRS on pain, function, and depression</i>	<i>Understand factor that may influence treatment outcomes</i>
<i>To examine impact of EFAR on stigma</i>	<i>Stigma changes over the course of treatment</i>	<i>Possible benefit of intervention</i>
<i>Qualitative information to inform treatment development</i>	<i>Qualitative interviews prior to onset of treatment and following study phase one</i>	<i>Maximize effect of intervention</i>

4 STUDY DESIGN

4.1 OVERALL DESIGN

Central Hypothesis: Combination therapy with AD+EFAR is the most effective treatment compared to individual treatment.

To determine if single treatment with antidepressants (AD) or fear avoidance rehabilitation (EFAR), vs. the combination of the two is the better treatment for chronic low back pain patients with high negative affect. This study will also identify which patients are most likely to respond to components of the intervention and obtain qualitative information to inform treatment development.

Specific Aims

1. To compare the effectiveness of combination therapy with AD+EFAR vs. single treatment to improve pain, self-reported function, and depression in patients with chronic low back pain and high negative affect.

Hypothesis 1: AD+EFAR will show the most improvement in pain, function, and depression compared to AD or EFAR alone, with opioid use moderating a less robust response to any treatment.

Hypothesis 2: AD+EFAR will be the most effective in preventing opioid misuse and will be associated with greater reductions in daily opioid dose vs. AD or EFAR alone.

2. To identify predictors of treatment responses.

Hypothesis 3: Higher depression subjects will respond best to ADs and worse functioning subjects to EFAR.

Hypothesis 4: Improvements in conditioned pain modulation (CPM) will precede to improvements in pain and mediate treatment responses.

Hypothesis 5: Higher levels of IHRS will be associated with poorer treatment outcomes.

3. To examine impact of EFAR on IHRS.

Hypothesis 6: Efar, alone or in combination with AD, will improve IHRS.

4. To obtain qualitative information to inform future development of EFAR intervention to reduce stigma.

We are proposing a randomized, proof of concept study because the effectiveness of AD+EFAR needs better evaluation first under more controlled conditions. This is a phase 2 trial and will be coordinated at multi-sites: University of Pittsburgh, Brigham and Women's Hospital, and Mayo Clinic. 330 subjects will be recruited across all treatment arms and treatment sites. Randomization will be sub-stratified into those prescribed opioids at study entry (estimated to be approximately 30-35 per group; 95-105 total across 3 treatment arms) and those who are not on opioids (195-205). Participants are randomized to four months of antidepressant treatment (ADs), enhanced fear avoidance rehabilitation (EFAR), or the combination (AD +EFAR). After four months, those in the AD or EFAR groups who are not meeting the minimal clinical benchmark for pain and function improvement will be re-randomized to either continue the treatment they have had for four months or to the other treatment arm for four additional months. Non-responders randomized to continue the same treatment will continue with AD medication with no additional study visits or AD visits. If subjects prefer to continue having AD visits via phone call for the second half of the study (Phase 2), this will be noted and support will be provided by the study psychiatrist or nurse practitioner. Non-responders randomized to the other treatment arm will refer to the Week 1-16 Study Schedule to complete AD or EFAR visits with no additional study visits for Phase 2 of the study. The AD and EFAR subjects in the first four months who have met the clinical improvement benchmark will continue with that treatment at home for another four months, for a total of 8 months study duration. This involves remaining at the same dose of the AD or doing the home exercise program and use of the mobile app for EFAR. This adaptive, re-randomization component will increase the

number of treatment responders to each individual treatment (AD or EFAR) available for analysis for Aim 2 (predictors of treatment responses to each treatment).

In the AD+EFAR arm, participants will complete the AD medication dose titration and the EFAR sessions within four months and then continue to be tracked for an additional four months, for a total of 8 months study duration. In this second four month tracking phase, participants will continue on the AD at the same dose and continue with the home exercise program including use of the mobile app to boost engagement with EFAR. Re-randomization at the end of Month 4 will be made only for the AD or EFAR arms. Participants in the AD+EFAR arm will receive the same treatment throughout the 8-month study without re-randomization.

An interim analysis is planned to solely analyze responders vs. non-responders in order to determine which participants are re-randomized into Phase 2 of the study. This will be done at the end of Month 4 for each subject. This interim analysis is not an analysis of the aggregate trial data and thus is not considered an issue for the sample size calculations.

The primary outcome is the proportion of Composite responders, patients who had clinically significant improvements in pain, function, and depression. To operationalize, pain and function changes are joined into a calculated measure of “pain+function” response, which is common in pain trials. *A participant could be a pain+function responder, a depression responder, both, or neither.* There are two sub-components to this measure, the proportion of combined responders (pain + function benchmark responders) and depression responders.

In addition, subjects already prescribed opioids at study entry will have the option of slowly weaning their opioids voluntarily with medical supervision by one of the study physicians. Success with the wean is tracked as a secondary outcome. Additionally, common sources of bias and error are minimized by using: randomized group assignment, repeated weekly outcome variable assessment over time completed by the patient themselves at home, and active methods to maximize retention, such as the phone, email, and texting contact procedures.

There will also be an optional qualitative component to the study. A subset of 60 participants from the trial will be recruited to participate in two qualitative interviews. Sampling will be purposeful in order to maximize the richness and diversity of participant data including geographical location, age, race, ethnicity, sex, and use of opioid medications. Those participating in the qualitative component of the study will complete two 60-90 minute interviews, one prior to the initiation of treatment and the second in the two weeks following completion of phase one of the study. The interviews will be conducted using open-ended, inductive questioning organized around broad topics identified and piloted among the research team. Topics for the baseline interview will include participants’ experiences of public stigma, their own stigmatic beliefs, perceived causes and sources of stigma, and how they believe stigma can be addressed. Topics for the follow-up interview will include changes in stigma over the course of the intervention, if and how the intervention improved their stigma, and what they would like to see in future interventions that address the impact of stigma on patients with CLBP and high NA. Due to the geographical spread of study participants, all interviews will be conducted via telephone or videoconferencing software. Interviews will be digitally recorded and transcribed verbatim.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

There is a strong scientific premise for comparing the effectiveness of multimodal AD+EFAR with either therapy alone to improve pain, function, depression, and reduce opioid misuse in patients with CLBP and high NA.

Current Multimodal Treatments in CLBP

Smeets and his colleagues did not find significant differences in the improved outcomes amongst 212 CLBP subjects randomized to aerobic exercise, cognitive behavioral therapy, or their combination.[71] Pires and his colleagues found no added benefit of pain education in a trial of 55 subjects randomized to aqua therapy vs. aqua therapy+pain education.[72] In 69 CLBP subjects randomized to mindfulness meditation, cognitive psychotherapy, or the combination. Jensen and his colleagues found no significant differences between groups for improvements seen in pain, function, or depression at 3 or 6 months.[73] These findings all suggest that targeting the right patients for multimodal therapy and using the right combination of treatments are crucial. Hence, there is tremendous room for innovation and improvement in the development of better multimodal treatments for high impact chronic pain, and particularly in those with CLBP and high NA. This is the central gap in care we address in this proposal.

Dr. Mark Jensen provides a compelling theoretical and experimental model for the relationships between negative affect, depression, fear avoidance of pain, and the psychological behavioral inhibition system (BIS), which is the behavioral tendency to avoid harm, such as pain.[9, 74, 75] This work has shown that behavioral inhibition tendencies have correlations and structural equation model coefficients to NA, depression, and fear avoidance from .30-.50, indicating a moderate effect of greater behavioral inhibition (such as poor activity and function) to worsen NA, depression, and fear avoidance. This model suggests that treatments targeting behavioral inhibition through increasing behavioral activation (such as with fear-avoidance PT, specifically)[9] are most likely to improve NA, depression, and downstream pain and function.

In sum, this proposal is significant because the prevalent group of CLBP patients with high NA are vulnerable to a range of poor outcomes vs. those with low NA, including: higher pain, worse function, a greater likelihood of being prescribed opioids, increased opioid misuse, and are at a greater risk of opioid overdose, addiction, and death. These phenomena underscore the importance of NA as a treatment target and the necessity to address the unmet need for better comprehensive pain care in CLBP patients with high NA. This need is fueled by a lack of effective multimodal treatments that promote better behavioral activation.

Preliminary Data

There is a strong scientific premise for comparing the effectiveness of multimodal AD+EFAR with either therapy alone to improve pain, function, depression, and reduce opioid misuse in patients with CLBP and high NA. The preliminary data supporting this study is substantial and has helped build the basis of this study.[163] Large randomized controlled trials have been published and tested the separate components of our combined intervention (antidepressant medication and graded exposure PT/OT) which have shown improved pain, function, and NA symptoms.[10, 12, 82-84] More specifically, the SCAMP trial (Stepped Care for Affective Disorders and Musculoskeletal Pain) is the basis for our sample size calculation, the antidepressant medication portion of the study, and our criteria for pain and negative affect responders.[88,89] This study will be following the antidepressant treatment protocol of the SCAMP trial. The trial tested AD and pain self-management education in sequential order vs. usual care. SCAMP enrolled 250 patients either on or off opioids, with CLBP or knee pain and high NA.[10, 88, 89] At 6 months, 47% of the 123 intervention subjects had at least 30% improvement in average daily pain and function,[85] or at least 50% improvement in depression symptoms. There were 29% who were

combined pain, function, and depression responders vs. 10% in the usual care group. At just 4 months, the vast majority of responders had reached these benchmarks and maintained this level of response sustained up to the 1 year duration of the study. These are clinically meaningful but modest effects and without combination therapy.

Additionally, Dr. Karp conducted the randomized trial, “Addressing Depression and Pain Together” (ADAPT)[11] which randomized 227 older adults with CLBP and major depression to venlafaxine +/- problem solving psychotherapy, and both were delivered by nurse practitioners. In Phase 1, if subjects did not respond to 6 weeks of lower dose venlafaxine (an SNRI), they were randomized in Phase 2 to higher dose venlafaxine or venlafaxine + problem solving psychotherapy. A response metric of combined pain and mood responders was the same as in SCAMP (>30% improvement in pain and >50% in depression). There was a 64% (145/227) study completion rate at 1 year and 100/227 responded (44%). There were no differences in response rates between treatment arms or phases. These results indicate that problem solving psychotherapy was NOT additive to venlafaxine alone to improve depression and pain. Of note, 96 subjects were co-prescribed opioids (42%), and they had an average 21% improvement in pain. which is less of a response than the non-opioid group.

Randomized trials of 6 months duration by Dr. Steve George have shown the effectiveness of 2 months of this PT vs. usual care in reducing NA and pain in low back pain patients on or off opioids.[12, 90] These two randomized controlled trials enrolled 174 patients and had an average 70% treatment completion and study retention rate at six months. The 67 patients receiving fear avoidance-based PT (FABPT) had an average 59% improvement in pain, 40% improvement in fear avoidance beliefs, and 58% improvement in self-reported function vs. smaller changes with usual care ($p < .05$). These studies and others have demonstrated that the improvements in pain reported after FABPT are mediated by decreasing NA.[91, 84]

What seems clear from the SCAMP, ADAPT, and PT trials is that the key ingredients to improving negative affect and pain are ADs, pain education, and FABPT. While there are efficacy data for each of these modalities alone vs. usual care,[10, 12, 90, 92, 93] there are no head-to-head efficacy comparisons of these treatments. In response, we did a 4-month randomized pilot trial at University of Pittsburgh to examine the effectiveness of these 4 treatment arms: pain education, ADs, FABPT, and the combination of AD+FABPT. The study enrolled 71 subjects with CLBP and high NA who may or may not be prescribed opioids. We compared measures of combined pain+function and depression responses. Results showed that AD+FABPT had a 40% responder rate for pain+function and a 75% responder rate for depression. The findings for AD+FABPT from the pilot study were better than in the SCAMP trial; thus, suggesting that AD+FABPT is a good approach and an effective combination therapy for CLBP patients with high NA. Our intervention development for this proposed study combines the efficacy from several multimodal approaches to maximize multimodal treatment success.

4.3 JUSTIFICATION FOR DOSE

We are using a modified version of the antidepressant treatment protocol of the SCAMP trial (Stepped Care for Affective Disorders and Musculoskeletal Pain - published in JAMA 2009), which optimized antidepressant (AD) therapy. It was not wedded to a strict hierarchical algorithm because only a third of patients started on any particular AD achieve remission, and there is no strong evidence that one AD is superior to another. SCAMP optimized AD therapy in line with common clinical practices and thus, is the basis of our medication protocol. Just as in SCAMP, trained nurse practitioners will do the primary

prescribing. A study psychiatrist will be available to the nurse practitioners to oversee the prescribing, address any concerns of the nurse practitioners, and see participants face-to-face if needed.

We follow a similar patient contact schedule and medication adjustment parameters as in SCAMP at weeks 2 (start of AD, in-person visit), and every 2 weeks thereafter at weeks 4, 6, 8, 10, 12, 14, and 16 via telephone contact, in which the study prescriber discusses the medication and makes adjustments. The phone call is structured to discuss symptoms, side effects, dose adjustments, and lasts at least 10 minutes. The new prescription will then be available to the subject. Further details about the prescribing of antidepressant medication will be included in **Section 8.1, Treatment Arm 1: Antidepressant (AD)** on the MOP.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the 4 month initial treatment phase. The 2nd 4 month block is for longitudinal tracking purposes (AD+EFAR arm) and to better identify predictors of response (AD or EFAR alone arms with re-randomization of non-responders). All phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

Pre-screening procedures will be performed under a separate phone screening form. In addition, some of the inclusion criteria will be determined by assessments collected at Study Visit 1 after the participant has signed the consent form. These assessments include PHQ-4, PROMIS 2-item cognitive screener, TAPS Tool, urine toxicology, and/or urine pregnancy test. If the participant does not meet all the above criteria, he/she will not be eligible for study participation and will be withdrawn from the study.

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Male or female, aged 18-75
- Pain duration > 6 months
- Must meet the minimum criteria for cognitive function using the PROMIS 2-item cognitive screener (>3)
- Average pain score of > 3/10, with low back pain being the primary pain site
- CLBP meeting Quebec Task Force Classification System categories I-III (from axial pain only to pain radiating beyond the knee without neurological signs). Constant radicular pain associated with sensory loss is highly treatment resistant without surgery
- In the investigator's judgment, evidence of healthcare seeking for low back pain
- Must meet criteria for high negative affect at 1st study visit: at least 5 on the PHQ-4 (also called the PHQ-2 + GAD-2). At visit 1, PHQ-4 score cannot be decreased to less than 3. This is to acknowledge that PHQ-4 scores can vary from day-to-day. Scores above 5 are highly associated with having a co-morbid major depression or generalized anxiety disorder diagnosis. An elevated PHQ score is used as a proxy for high scores on the PROMIS depression and anxiety measures.
- Having accessible electronic medical records from UPMC, Brigham and Women's Hospital, or Mayo Clinic, Rochester.

- For those taking opioids (the opioid subgroup), they must be prescribed opioids currently for at least 3 consecutive months prior to enrollment. Patients must be on opioids for a minimum of three months, taking them on a daily basis or intermittently during the week. We will include those on strong opioids, such as oxycodone and weak opioids, such as tramadol
- Subject must agree that opioids cannot be increased during the study
- For those taking opioids (the opioid subgroup), no active substance use disorder in the past year as determined by the PI with the use of the Tobacco, Alcohol, Prescription Medications, and Other Substance Tool (TAPS) and a urine toxicology screen. The exceptions are tobacco, medical marijuana use in Pennsylvania or Minnesota, recreational or medical marijuana in the Boston site, or mild prescription opioid use disorder such as opioid misuse
- No acute suicidality or history of major thought disorder (such as mania or psychosis). This will be assessed at study entry which will also include a review of history in EPIC/EMR
- Must possess a mobile device or tablet that can send and receive text messages and access the internet

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Back surgery within the past six months
- Active worker's compensation or litigation claims
- New pain and/or psychiatric treatments within 2 weeks of enrollment
- At the PI's discretion, intent to add new or increase pain treatments during the study period, such as back surgery, nerve block procedures, or medications
- At the PI's discretion, intent to add new psychiatric treatments during the first 4 months of the study
- Any clinically unstable systemic illness that is judged to interfere with the trial
- History of cardiac, nervous system, or respiratory disease that, in the investigator's judgment, precludes participation in the study because of a heightened potential for respiratory depression
- Non-ambulatory status
- Pregnancy or the intent to become pregnant during the study. Women of childbearing potential will all submit a urine sample pregnancy testing at enrollment (AD or AD+EFAR)
- Not fluent in English and/or not able to complete the questionnaires

Children less than 18 years of age are excluded due to rare occasions for children to have chronic low back pain.[181] It also remains uncertain when to use antidepressant medication to treat children with depression or anxiety disorders.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Refrain from increasing opioids increased during the study
- Participants who is pregnant or intend to become pregnant during the study duration will be excluded from the study.
- Abstain from adding new or increased pain treatments during the study period, such as back surgery, nerve block procedures, or medications.

- Refrain from adding new psychiatric treatments during the first 4 months of the study

If the following prohibited procedures and treatments are indicated for care, the site PI will determine if the participant is suitable for study participation. It is possible that this may lead to an early withdrawal if participants are unable to follow the daily tasks/criteria required by the study, if any safety concerns arise, or if information is obtained that indicates the participant does not meet eligibility requirements for inclusion in the study.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this trial after the results of testing in Visit 1 (screen failure) will not be rescreened. We will track screen failures as part of the CONSORT diagram process.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Summary of sample size and source of recruitment:

- Target study sample size: 330; takes into account the higher than anticipated drop-out and study withdrawal rate for the study
- Anticipated number of participants to be screened/enrolled: 1200
- Source of participants: outpatient clinics, hospital setting, general public
- We expect at least 50% enrollment from females and 18% from minorities

Recruitment Methods

Patients will be recruited from the Brigham and Women's Hospital, Mayo Clinic, and University of Pittsburgh's UPMC pain clinics, and primary care clinics. Recruitment strategies will be slightly different across the 3 study sites. The investigators may directly recruit by approaching their own patients, outreaching to primary care physicians in the community, and using a variety of strategies described below. If a physician is aware of a potential participant, the physician will briefly inform the participant of a low back pain research study and ask the participant for permission to be called by the study team. This permission will be documented in the medical chart, if necessary per local IRB requirements. The research team can then approach the patient to explain the study. The study sites may also contact potential participants from previous studies that have requested to be contacted about new studies. The study team will make an attempt to prescreen interested participants for eligibility purposes at the time of contact. The screening form will be used to prescreen subjects prior to Study Visit 1. This can be used for in-person or telephone contact.

Flyers will be posted in the clinic waiting rooms and exam rooms with instructions to call, email or text the study coordinators to indicate interest in their study. Research registries of volunteers, best practice alerts in the electronic medical record, and electronic blogs or Facebook pages will be used as well. Efforts will be made to attain a mix of study participants, in terms of gender and racial/ethnic representation reflective of the population of the greater metropolitan Pittsburgh, Boston, and

Rochester area. We will review our patient demographic distribution quarterly and if we find that our gender or minority recruitment is lagging we will initiate targeted recruitment strategies to increase gender or minority representation.

Participant Retention

Every effort will be made by the PI and study team to ensure participants complete each study visit and the study overall. We will use the following strategies to help maximize retention and minimize loss to follow-up:

- Following a proactive plan for retention, including calling and meeting with participants to see how they are doing, and providing transportation and parking remuneration of \$100 for Phase 1 and \$100 for Phase 2. Transportation and parking remuneration will be available to subjects only at the Pitt and Mayo Clinic study site as Brigham and Women's Hospital normally doesn't provide remuneration for parking and transportation.
- If a participant drops out or is withdrawn from the study, they will receive transportation and parking remuneration based on the number of weeks they complete.
- Building participant relations and participant satisfaction, with the study coordinator taking a central role on this effort e.g., the study coordinator providing a two-way communication via Mosio text messaging system, reminding the participant to complete weekly REDCap surveys during the study and offering an accessible platform for effective communication
- Ensuring subject compliance by covering the costs of all antidepressant medication and EFAR sessions, and compensating for each study visit 1-4
- Giving participants the opportunity to ask questions and express concerns pertaining to their condition during scheduled visits
- Enhancing participant's understanding of the study's objectives and the protocol by ensuring to answer any questions the participant has during each clinic visit

In the event that a participant has missed 2 study visits, the PI and/or study coordinator will make 4 attempts to contact the participant using the contact information provided by the participant. If the participant can't be reached after the 4 attempts or for more than a month, the participant will be considered lost to follow-up. Missed visits will not be considered as protocol deviations.

Study Remuneration

Antidepressant only Group will receive up to \$370, detailed as follows:

Week 1 (Study Visit 1): \$30

Week 2 (Study Visit 2): \$30

Week 1-2 (Qualitative Interview 1): \$25

Week 8 (Study Visit 3): \$30

Week 16 (Study Visit 4): \$70

Week 16-18 (Qualitative Interview 2): \$25

Week 17-32 (8 Online Surveys): \$10 per completion of a weekly survey; up to \$80

Week 20 (Completion of Month 5 Visits): \$20

Week 24 (Completion of Month 6 Visits): \$20

Week 28 (Completion of Month 7 Visits): \$20

Week 32 (Completion of Month 8 Visits): \$20

EFAR only Group will receive up to \$490, detailed as follows:

Week 1 (Study Visit 1): \$30

Week 2 (Study Visit 2+PT1): \$30
Week 1-2 (Qualitative Interview 1): \$25
Week 8 (Study Visit 3): \$30
Week 16 (Study Visit 4 + completion of PT visits): \$70 + \$120
Week 16-18 (Qualitative Interview 2): \$25
Week 17-32 (8 Online Surveys): \$10 per completion of a weekly survey; up to \$80
Week 20 (Completion of Month 5 Visits): \$20
Week 24 (Completion of Month 6 Visits): \$20
Week 28 (Completion of Month 7 Visits): \$20
Week 32 (Completion of Month 8 Visits): \$20

***SUBJECTS MUST ATTEND ALL
WEEKLY STUDY EVENTS TO
RECEIVE FULL COMPENSATION
FOR THAT WEEK.***

AD+EFAR only Group will receive up to \$490, detailed as follows:

Week 1 (Study Visit 1): \$30
Week 2 (Study Visit 2): \$30
Week 1-2 (Qualitative Interview 1): \$25
Week 8 (Study Visit 3): \$30
Week 16 (Study Visit 4 + completion of PT visits): \$70 + \$120

Week 16-18 (Qualitative Interview 2): \$25
Week 17-32 (8 Online Surveys): \$10 per completion of a weekly survey; up to \$80
Week 20 (Completion of Month 5 Visits): \$20
Week 24 (Completion of Month 6 Visits): \$20
Week 28 (Completion of Month 7 Visits): \$20
Week 32 (Completion of Month 8 Visits): \$20

Non-responders that are re-randomized to receive a new treatment for Phase 2 of the study will receive \$20 at the end of Month 5, 6, 7, and 8 for those who complete all study items and visits for that month. Completion of biweekly online surveys during Phase 2 will also be rewarded at \$10 per completion of each biweekly online survey. This totals another \$160 as compensation for subjects.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTIONS ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Treatment Arm 1: Antidepressant (AD)

The study intervention for Antidepressant treatment implements the use of AD medication in order to potentially improve pain, function, and depression outcomes.

- The participant will be prescribed antidepressants during their Study Visit 2. Medication will be shipped to the participant's address by the study Pharmacy that dispenses the medication.
- The participant will complete weekly surveys at home via email, and some surveys relevant to AD treatment will be obtained every other week, such as the FIBSER, PHQ-9 and AD Side Effects Checklist to record any indicators of side effects and discomfort.

- The nurse practitioner will follow the AD Visit schedule and reach out to participants via phone call to ensure time for participants to express concerns pertaining to their treatment. The nurse practitioner will then review the FIBSER, PHQ-9 and AD Side Effects Checklist together with participant at each AD Visit and discuss any instances of discomfort in order to adjust their current medication. There will be a total of 7 AD follow-up visits, which can be completed via phone or in-person.
- Non-responders determined at the end of Week 14 will be re-randomized to continue receiving current treatment or EFAR for Phase 2 of the study.

Treatment Arm 2: Enhanced Fear Avoidance Rehabilitation (EFAR)

The study intervention for EFAR treatment implements the use of physical/occupational therapy and pain education in order to potentially improve pain, function, and depression outcomes.

- The participant will engage in gradual exposure to exercises and activities they are apprehensive about, such as standing to wash dishes. These sessions are delivered by a trained physical or occupational therapist. Max no-show rate for EFAR visits is 4.
- The participant will be provided verbal and written educational material regarding chronic low back pain and fear of movement to review at-home. The understanding of these topics is aimed to reduce fear avoidance behaviors.
- Participants will complete the FDAQ prior to each EFAR session. The FDAQ will determine the degree of graded exposure in the functional activities for that EFAR session.
- Non-responders determined at the end of Week 14 will be re-randomized to continue receiving current treatment or AD for Phase 2 of the study.

Treatment Arm 3: Antidepressant and Enhanced Fear Avoidance Rehabilitation (AD+EFAR)

The study intervention for AD+EFAR Treatment implements the use of BOTH antidepressant medication, and physical/occupational therapy and pain education in order to potentially improve pain, function, and depression outcomes.

- Subjects will receive both antidepressants and EFAR treatment simultaneously as compared to the individual treatments. AD treatment will start in Week 2 and EFAR treatment will start at Week 4.
- No re-randomization will be done for this treatment arm. Participants will continue receiving the treatment for 8 months.

Opioid-Weaning Procedures

Subjects prescribed opioids prior to study entry will undergo sub-stratified randomization and their outcomes will be tracked separately in addition to the aggregate outcomes for the entire study cohort. The choice to be weaned is voluntary and at each subject's own pace, in discussion with the study opioid prescriber.

- Subjects will have to first sign an opioid therapy agreement on Study Visit 1, if they haven't in the past.
- It is mandatory for subjects taking opioids to attend the first Opioid Weaning Visit at the end of Week 4 and meet with the study physician. (this can be completed via phone call.)
- After Opioid Weaning Visit 1, subjects will have a choice on whether they want to attend Opioid Weaning Visits 2-4. These visits can be in-person or mobile.

6.1.2 DOSING AND ADMINISTRATION

For all medication treatment the study team will instruct the patient on what to do if a dose is missed or delayed. In general these events do not result in significant consequences.

Procedure for Selection Each Participant's Antidepressant Treatment and Dose

- 1. Initial assessment choice of antidepressant treatment** – The NP or psychiatrist will use the Antidepressant Treatment History Form (ATHF) as a general guide to assess which antidepressants to prescribe. Adequacy of any prior antidepressant medication treatment will be considered to assist with the choice of AD.
- 2. Choice of antidepressant treatment** – Patients who are not taking any antidepressant (AD) at study entry will start at Step 1 as detailed in the Medication Flowchart below. Patients who are currently prescribed an AD will be assessed regarding if the current AD or augmentation agent is subtherapeutic and dosed inadequately. If so, these dose(s) can be increased. The study prescriber will coordinate with the current treating provider to increase the dose(s) appropriately. If participants are already on an appropriate dose, then they are weaned off of the AD by the study prescriber over 1-2 weeks and a new one is started according to the flexible algorithm. Because participants have high levels of depression and anxiety to qualify for study entry, by definition such an AD taken by the subjects at a suitable dose at study entry is deemed ineffective and a new one is started. Although unlikely, it is possible that a subject could be on an AD at a suitable dose which improved pain, but not depression or anxiety, since ADs can improve pain independent of mood effects. In this scenario, the study prescriber will proceed to Step 4 (options 1-3), augmentation of AD.
- 3. AD Titration following AD Visits** – The prescriber maximizes the AD dose as tolerated up to a clinical endpoint of at least 50% improvement in depression or anxiety symptoms. Partial responders to any of the medications prescribed at a tolerable dose in each of the steps can be prescribed any of the additional, augmentation medication options in step 5.

We follow a similar patient contact schedule and medication adjustment parameters as in SCAMP at weeks 2 (start of AD, in-person visit), and every 2 weeks thereafter at weeks 4, 6, 8, 10, 12, 14, and 16 via telephone contact, in which the study prescriber discusses the medication and makes adjustments. The phone call is structured to discuss symptoms, side effects, dose adjustments, and lasts at least 10 minutes. The new prescription is then mailed to the subject, and this system has worked well in our pilot study. For example, in Step 2 SNRI after 2 weeks if there is no response and the patient is tolerating the dose, that dose is increased. Participants are assessed every other week via the emailed surveys with PHQ-9, FIBSER and AD Side Effects Checklist to determine response, tolerability, and potential dose adjustment or medication change. The goal is to increase doses towards optimized dose at two-week intervals.

Medication Flowchart:

Step	Drug	Class	Indication	Initial Dosage (mg)	Max Dosage (mg)
Step 1: Optimize antidepressant pharmacotherapy that participants are on at study entry.					
1a:	Any current antidepressant or augmentation agent at	Variable	On medication at study entry	Variable	Maximize dose

suboptimal dose(s)					
1b: Partial response to optimized baseline pharmacotherapy, consider augmenting with bupropion or aripiprazole (see Step 4 below).					
1c: Non-response, proceed to Step 2.					
Step 2: SNRI: Select SNRI based on: 1) participant choice; 2) prior exposure, considering tolerability and benefit. If participant tried either medication, endorses that it was tolerable but dose was < 60 for duloxetine, < 150 for venlafaxine, and duration of exposure was < 6 weeks, consider re-trial. Given potential longer titration for venlafaxine, it can be increased by 37.5 or 75 mg increments every week instead of every 2 weeks.					
2a.	Duloxetine or Venlafaxine/ Venlafaxine ER	SNRI	First choice for first switch for patients with pain and depression	20 mg (duloxetine) 30 mg (duloxetine) 37.5 mg (venlafaxine XR) 75 mg (venlafaxine ER) 150 mg (venlafaxine ER)	120 120 300 300 300
2b: Partial response to optimized duloxetine or venlafaxine, consider augmenting with bupropion XL or aripiprazole.					
2c: Non-response, proceed to Step 3.					
Step 3: SSRI: Select SSRI based on: 1) participant choice; 2) prior exposure, considering tolerability and benefit. If participant tried either medication, endorses that it was tolerable but dose was < 20 for escitalopram, < 150 for sertraline, and duration of exposure was < 6 weeks, consider re-trial.					
3a.	Escitalopram	SSRI	Failed SNRI	5-10	20
3b.	Sertraline	SSRI	Failed 1 st SSRI	50	200
3c: Partial response to optimized escitalopram or sertraline, consider augmenting with bupropion XL or aripiprazole.					
3d: Non-response, proceed to Step 4.					
Step 4: Augmentation Agents/4th Line Agents					

4a.	Bupropion XL (cannot be co-prescribed tramadol; screen negative for seizure history) Bupropion SR	Other	Consider if weight gain, daytime fatigue/sleepiness.	150 100	450 450
4b.	Mirtazapine	Other	Consider if insomnia, decreased appetite or GI symptoms	7.5-15	60
4c	Aripiprazole	Atypical antipsychotic	Partial response to Steps 1-4a,b, augmentation agent	2.5-5	15
4d	Nortriptyline	TCA		50-75	300
4e	St. John's Wort	OTC SSRI	Consider if intolerance to other ADs, or per patient preference	300-600	900

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Study Coordinator will initiate randomization procedure by contacting the site's Investigational Drug Service (IDS) once a participant is deemed eligible for the study. The IDS will store the antidepressant medications and dispense them to the subjects after receiving order from the study team. University of Pittsburgh and Mayo Clinic IDS will ship the medications to the homes of each subject or they can be picked up upon request. At Brigham and Women's Hospital, the study coordinator will pick up the medication from IDS and arrange for delivery or pick up with the participant. These are not controlled substances.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

N/A

6.2.3 PRODUCT STORAGE AND STABILITY

The medications can be stored at room temperature and have a shelf life of greater than one year. Unused medications by the subjects can be returned to the study staff. We will provide a mechanism to have those mailed to us if there are no further in-person visits.

Product maintenance guidelines will be updated quarterly by the IDS. As guidelines are revised, new versions are provided to study teams with investigational products on the 1st of the month of the next quarter. Each version received will be stored securely in the study binder.

6.2.4 PREPARATION

Antidepressant

Antidepressant medication will be prepared by each study site's own Investigational Drug Service (IDS). After a patient is enrolled, the Study Coordinator at each site will inform their respective IDS.

EFAR Treatment

Physical/occupational therapists will review the contents of *Mayo Clinic Guide to Pain Relief* bookazine in preparation of providing pain education to participants during EFAR sessions. (Please refer to Section 11.3 EFAR Pain Education Outline in the Manual of Procedures for more details).

Conditioned Pain Modulation

Study team will be properly trained by the site PI to do this procedure. Prior to administering CPM to participants, study team staff will have to prepare a water bath for the testing.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization to each of the 3 treatment arms is a measure to minimize bias and error. **NO TREATMENTS** are blinded in this study. The study physicians are shielded from knowing which treatment group the subject is assigned to. The randomization procedure is as detailed:

Randomization Plan

Subjects are randomized after enrollment, which means after they are consented. 330 subjects will be recruited across all treatment arms and treatment sites to take into account the higher than anticipated drop-out and study withdrawal rate for the study. Thus, we will need 240 participants to complete this study. Randomization will be sub-stratified into those prescribed opioids at study entry (estimated to be approximately 30-35 per group; 95-105 total across 3 treatment arms) and those who are not on opioids (195-205).

The study coordinators will be doing the randomization at their respective sites on REDCap. The University of Pittsburgh will randomize 150 subjects, and Brigham and Mayo will randomize 75 subjects each in 1:1:1 ratios with blocks of 6.

Re-Randomization Plan

At the end of Week 15, the Study Coordinator will calculate the responder and non-responder criteria for re-randomization. Except, since these subjects can only be randomized to AD or EFAR, randomization

will be done in blocks of 4 in a 1:1 ratio. The biostatistician, Dr.Ma will oversee the overall randomization and re-randomization process.

Randomization and re-randomization will be done by the study coordinators at their respective sites on REDCap. The list will be uploaded onto REDCap, utilizing their randomization module that was developed by the study biostatistician.

In addition, non-responders in the AD or EFAR treatment will have a choice to continue their current treatment or be re-randomized to a different treatment. Those who were previously in the AD treatment and is switched to a different treatment will have the option of being weaned off of AD while receiving the new treatment. Responders in the AD or EFAR treatment who are also opioid-users will resume to their usual opioid prescriber at the end of Month 4. Non-responders that are re-randomized and are opioid-users will continue to receive opioid medication and opioid weaning guidelines from the study physician for an additional 4 months (Phase 2).

6.4 STUDY INTERVENTION COMPLIANCE

Study intervention compliance is defined by the completion of visits and assessments (e.g., weekly surveys via REDCap) by participants during the 8-month study duration. There are no study devices involved.

6.5 Concomitant Therapy

- **New pain or psychiatric medication** – Participants are asked not to take new pain or psychiatric medication other than the medication prescribed by the physician and/or nurse practitioner during the first 4 months of the study. Participants will be asked to complete the Medication Log weekly if they have started any new medication.
- **Increased pain medication** – Participants are asked not to increase other pain treatments during the study period, including back surgery, nerve block procedures, or medications.

The following includes all the medications that are allowed during the study:

- **Opioid medication** – Participants are advised to comply with only the pain medication and dosage that the study physician has advised for them for the duration of the study.
- **Antidepressant medication** – Participants are advised to comply with only the antidepressant medication and dosage that the study psychiatrist/nurse practitioner has prescribed for them. AD Visits will take place to ensure a suitable AD dosage for the participants.

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a licensed physician, physician assistant, and NP/psychiatrist. A Medication Log will be used to collect concomitant medication information such as the use of antidepressant, opioids, non-opioids, and therapeutic treatments. The Medication Log will be collected weekly for the entire duration of the study.

6.5.1 RESCUE MEDICINE

N/A

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Discontinuation from the study interventions does not mean discontinuation from the study, and remaining study procedures will be completed as indicated by the study protocol if the subject chooses to remain in the study. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- These subjects will follow the same data collection schedule as outlined in section 1.3 if they choose to remain in the study.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- EFAR physical therapy no-shows of 4 or more
- If any adverse event (AE), serious adverse event (SAE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant (e.g., back surgery, adding new treatments during the specified halt period). This will be decided in discussion with the 3 site PIs.
- Disease progression, in the investigator's judgment requires discontinuation of the study intervention such as cardiac or respiratory disease.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The rationale for participant discontinuation or withdrawal from the study will be recorded in RedCap Following their last visit or follow-up call. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted after 4 attempts or for more than a month by the study team staff.

The following actions must be taken if a participant fails to return to the clinic for 2 scheduled study visits:

- The site will attempt to contact the participant and reschedule the missed visit within 2 weeks timeframe from their last missed visit and counsel the participant on the importance of

maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study. Visits missed due to the site will be considered protocol deviations.

- Before a participant is deemed lost to follow-up, the site investigator or study team staff will make every effort to regain contact with the participant (where possible, 4 attempts via telephone calls or email and, if necessary, a certified letter to the participant's last known mailing address).
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Prescreening (prior to enrollment):

The phone screening is a basic screening done to see if potential participants are likely to meet eligibility prior to being consented. The Study Coordinator will pre-screen potential participants via telephone by asking brief questions regarding their medical history and the 4-item, Patient Health Questionnaire (PHQ-4) to screen for high levels of negative affect (score >5). A Waiver of Consent was requested to the IRB to obtain questions regarding participant's medical history, PHQ-4, and ability to complete the duration of the study prior to consenting.

The site PI or Nurse Practitioner (NP) will review the telephone screening form and the potential participants' medical records. The PI or the medical Sub-I will sign a separate form on RedCap attesting to having reviewed inclusion/exclusion criteria and confirming eligibility. Once the participant has met the basic criteria based on their answers recorded on phone screening form, the Study Coordinator will inform the participant and schedule them for Study Visit 1. In the case that the participant does not meet the inclusion/exclusion criteria (e.g. pain duration < 6 months, pain not primarily located in low back, participant does not agree to halt increasing opioids during the study), they will be stopped from further screening.

Screening at Visit 1: Upon arrival, the participant will first meet with a study staff to review and sign the informed consent. Baseline assessments will be collected by the NP/psychiatrist and study staff after the participant has signed the informed consent in the presence of a study coordinator. If it is determined that they do not meet all inclusion and exclusion criteria from the baseline assessments (e.g., PROMIS 2-item cognitive screener <3, PHQ-4 <5) they will be withdrawn from the study. (See Inclusion/Exclusion Criteria)

In the case that the participant is no longer interested in participating in the study, basic information regarding screen failures, the reason for the screen fail, will be recorded and retained for all participants who are screened.

This section includes a list and description of the following procedures/evaluations:

- **Urine collection and laboratory evaluations** will be done by a third-party laboratory to evaluate opiate levels and signs of substance use. All laboratory testing locations are appropriately licensed and comply under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88), as required by certain state laboratory licensure programs.
- **Administration of questionnaires or other instruments** for patient-reported outcomes, such as a PROMIS-29, Pain Catastrophizing Scale, Medication Log, Fear Avoidance Beliefs Questionnaire

will be administered by a study staff during study visits. In the case that participants choose to complete study visits via phone call, a survey link will be sent to them to complete surveys at home.

- **Study visits** will be completed by the nurse practitioner, study physician, and/or study staff to assess participant's overall progress and side effects, and to adjust dosage accordingly.
- **AD visits** will be completed by psychiatrist/nurse practitioner to record side effects of antidepressants, answer participant concerns, and adjust dosage accordingly.
- **Opioid-weaning visits** will be completed by the study physician to discuss side effects and adjust opioid-weaning guidelines, as needed.
- **EFAR visits** for EFAR and AD+EFAR treatment group will be completed by physical/occupational therapists as part of physical/occupational therapy and pain education.
- **Conditioned pain modulation** will be completed by study staff for opioid-users

For more details on the sequence of visits, please review **Section 11.2 Study Visit Procedures** of the MOP.

8.2 SAFETY AND OTHER ASSESSMENTS

This section may include a list and description of the following procedures/evaluations to be done as part of the study to monitor safety:

- **Urine collection, pregnancy test, and laboratory evaluations** will be done by a third-party laboratory to evaluate opiate levels and signs of substance use. A urine pregnancy dipstick test will also be completed by participants randomized to receive antidepressant medication to ensure participant's safety of the study intervention. Potential risks associated with antidepressant medication and pregnancy will be discussed with female participants of childbearing age during the informed consent process. These participants will be instructed to contact the PI immediately if they believe there may be a change in pregnancy status at any time throughout the duration of the study.
- **Adequate visits** will be provided for participants to share their progress and concerns about the treatment. They will also have the opportunity to ask questions during study visits, AD visits, EFAR visits, and opioid-weaning visits.
- **Assessment of study intervention adherence** or see Study Intervention Compliance, section 6.4
- **Administration of questionnaires** to record potential side effects, such as Medication Log, Opioid Side Effect Checklist, PHQ-4, and PHQ-9.
- **Assessment of adverse events.** Study physician and NP will ask the participants every study visit regarding the occurrence of adverse events. Added safety measures include the collection of Columbia-Suicide Severity Rating Scale (CSSRS) to monitor medication side effects including suicidality. Suicidality is also assessed every other week through the PHQ-9, question 9 regarding thoughts about death. Scores on this item >1 (thoughts about dying more than half the days or every day of the week) will be followed up by the nurse practitioner at the AD adjustment phone calls to assess the level of suicidal intent. Any PHQ-9, question 9 score of 3 at any rating point ("thoughts about dying nearly every day") will also automatically trigger administration of the Columbia Suicide Severity Rating Scale (CSSRS). In the case of a possible psychiatric emergency, the nurse practitioner will confer with the study psychiatrist to determine the next steps. The prescribers are clinically trained to handle these situations and patients will be immediately referred to emergency medical services if needed.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 Definition of Adverse Events (AE)

An adverse event is any unfavorable and unintended diagnosis, sign including an abnormal laboratory finding, symptom, or disease temporarily associated with the study intervention, whether or not considered intervention related. AEs include any new events that are not present during the pre-intervention period or events that were present during the pre-intervention period which increased in severity (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event is any untoward medical occurrence if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly/birth defects, other significant hazards, or potentially serious harm to research participants or others. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32 (a)).

8.3.3 Classification of an Adverse Event

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events does not impact the participant's health in any way.
- **Moderate** – Events impact the participant's health but is not life-threatening or incapacitating.
- **Severe** – Events are permanently disabling, severely incapacitating, or may require prolongation of existing hospitalization.
- **Life-threatening** – Events are fatal and life-threatening.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) will have their relationship to study intervention assessed by the site PI who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be assessed using the level of specificity below. In a clinical trial, the study product must always be suspect.

- **Not related** – Event is clearly related to factors such as the subject's clinical state, not with therapeutic interventions associated with the study protocol.

- **Unlikely related** – Event was most likely related to factors such as the subject's clinical state, not with therapeutic interventions associated with the study protocol.
- **Possibly related** – Event follows a reasonable temporal sequence from initiating the participation and/or is consistent with known events related to the study treatments, or participation in cognitive assessments or sensory testing, but it is possibly related to factors such as the subject's clinical state.
- **Probably related** – Event follows a reasonable temporal sequence from initiating the participation and/or is consistent with known events related to the study treatments, or participation in cognitive assessments and cannot be reasonably explained by factors such as the subject's clinical state.
- **Definitely related** – Event follows a reasonable temporal sequence from initiating the participation and/or is consistent with known events related to study treatments, or participation in cognitive assessments or sensory testing and cannot be reasonably explained by factors such as the subject's clinical state. In addition, the event occurs immediately following the treatment or study visit, improves on stopping the treatment or any of the tasks performed during the study visit, or reappears once treatment or study tasks are resumed.

8.3.3.3 EXPECTEDNESS

Site PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits or study intervention of a study participant presenting for medical care, or upon notification from participant via phone call, email, or text. These subjects will remain in the study if possible and their clinical course will continue to be tracked. All of the medications are FDA approved for the treatment of depression and thus documenting that an event occurred is more relevant in this study than tracking the duration of every AE.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed by NP, psychiatrist, and/or study physician), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. In the event that an AE continues past Week 16 or 32 for Phase 1 and 2 respectively, the stop date of the AE will be recorded as "unknown"/"ongoing".

Any medical condition that is present at the time that the participant is screened will be considered for participant eligibility and as baseline, and not reported as an AE. However, if it is determined by the investigators, NP/ psychiatrist, and/or study physician that the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of

onset and duration of each episode. At each study visit, the study physician and/or NP/ psychiatrist will inquire about the occurrence of AE/SAEs since the last visit. Serious Adverse Events will be followed for outcome information until resolution or stabilization, however, AEs will not be followed-up after it has been resolved.

Adverse Events

All AEs will be reported to the DSMB and the NIAMS as part of the semiannual routine report meeting.

Serious Adverse Events

All Serious Adverse Events (SAEs) regardless of relatedness or expectedness will be reported to the DSMB and NIAMS (via the NIAMS Executive Secretary) within 48 hours of the investigators becoming aware of the event. The PI will report the SAEs to the IRB within 5 business days of becoming aware of the event, according to local IRB requirement.

Protocol Deviation/Violation

Protocol deviations that impact participant safety should be reported to the NIAMS and DSMB (via the NIAMS Executive Secretary) within 48 hours of the investigator becoming aware of the event. Protocol deviations that do not impact participant safety should be reported in aggregate to the NIAMS and DSMB (via the NIAMS Executive Secretary) as part of the semiannual routine meeting report. Any major deviations to the protocol will immediately be reported to the local IRB within 5 business days.

Unanticipated Problems

All unanticipated problems regardless of whether they are SAEs or not will be reported to the NIAMS and DSMB (via the NIAMS Executive Secretary) within 48 hours of the investigator becoming aware of the event. The PI will report the UPs to the IRB within 5 business days of becoming aware of the event, according to local IRB requirement.

8.3.5 ADVERSE EVENT REPORTING

According to 21 CFR 312.64(b), the investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol. All nonserious adverse events will be reported to the DSMB and NIAMS on a semiannual basis for the routine DSM report meetings. Study team staff and study physicians will be trained to identify and to bring to the site-PIs any complaints or adverse reactions among participants. It is the responsibility of the research coordinator to notify the site PI and report the AE. The site PI will then notify the medical monitor and the local IRB. After advisement from the IRB, the site PI will determine study status in discussion with study PI.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study physician and/or study team staff will immediately report to the DSMB and NIAMS of any serious adverse event, whether or not considered study intervention related, including those listed in the protocol and will include an assessment of whether there is a reasonable possibility that the study intervention caused the event (21 CFR 312.64(b)). The investigator will immediately report all serious adverse events per occurrence regardless of relatedness or expectedness, including unanticipated problems to the DSMB and NIAMS (via the NIAMS Executive Secretary) within 48 hours of the

investigators becoming aware of the event. The PI will also report serious adverse events and unanticipated problems to the IRB within 5 business days of becoming aware of the event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event requested by the DSMB and/or NIAMS will be provided as soon as possible.

The study investigators will be responsible for notifying the Food and Drug Administration (FDA) of any serious, unexpected adverse experiences from all sources (domestic and foreign) as soon as possible, but in no case later than 15 calendar days of initial receipt of the information by the investigator. For additional details, please refer to [FDA's Post-Marketing Reporting Guidelines](#).

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

The research procedures (e.g., antidepressant medication) will pose a physical or clinically significant psychological risk to women who are or may be pregnant; and thus, those who are pregnant or have the intent to become pregnant during the study duration will be excluded from the study as outlined in the Exclusion Criteria. Female participants of childbearing potential will receive a urine pregnancy test as part of the initial screening. Women of childbearing age who are placed in the AD or AD+EFAR Treatment Arm are required to take a urine pregnancy test prior to study treatment. Potential risks associated with antidepressant medication and pregnancy will be discussed with female participants of childbearing age during the informed consent process.

Participants will be instructed to contact the PI immediately if they believe there may be a change in pregnancy status at any time throughout the duration of the study. In this case, the site PI may decide to discontinue their study intervention and continue safety follow-up. This will be reported appropriately to DSMB, NIAMS, and IRB as needed.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated problems (UP) is defined by risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research. *Possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline (45 CFR part 46 guidance):

- All UPs will be reported to the NIAMS and DSMB (via the NIAMS Executive Secretary) within 48 hours of the site investigator becoming aware of the event.
- The PI will report the UPs to the IRB within 5 business days of becoming aware of the event, according to local IRB requirement.

Other UPs may warrant corrective actions at a specific study site. These corrective actions or changes will be considered by the site-PIs and leading PI in response to an UP:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Modification of informed consent documents to include a description of newly recognized risks and/or additional information about newly recognized risks to previously enrolled participants.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

There will be a formal Statistical Analysis Plan (SAP) to include additional statistical analysis detail. A formal SAP will be completed prior to database lock.

9.1 STATISTICAL HYPOTHESES

Primary AIM	To compare the effectiveness of combination therapy with AD+EFAR vs. each treatment alone to improve pain, self-reported function, depression, and anxiety in patients with chronic low back pain and high negative affect.
Secondary	To identify predictors of treatment responses.
Exploratory	To obtain qualitative feedback from participants that will inform the development of an intervention to reduce the impact of stigma
Endpoints:	<p>PRIMARY ENDPOINT: <i>Hypothesis 1</i>: AD+EFAR will show the most improvement in pain, function, and depression compared to single treatment with AD or EFAR alone, with opioid use moderating a less robust response to any treatment.</p> <p>The primary outcome is a composite response measure of changes in pain, function, and depression. There are two sub-component measures: the rate of pain+ function responders and the rate of depression responders in each group. A participant could be a pain+function responder, a depression responder, both, or neither.</p> <p>SECONDARY ENDPOINT: <i>Hypothesis 2</i>: AD+EFAR will be the most effective in preventing opioid misuse and will be associated with greater reductions in daily opioid dose vs. AD or EFAR alone.</p> <p>Secondary outcomes include changes in opioid misuse, opioid dose, sleep, anxiety, pain interference, and a variety of patient reported outcomes.</p> <p>EXPLORATORY ENDPOINT: Qualitative feedback obtained in two qualitative interviews, one prior to the start of treatment and one following the first phase of treatment, for an analysis of stigma-related issues.</p>

9.2 SAMPLE SIZE DETERMINATION

Sample size calculations are based on the AD+FABPT RCT and the Usual Care vs. EFAR pilot data. Despite being pilot data, these results were consistent with the SCAMP and ADAPT trials and thus are a good basis of data for sample size calculations. We hypothesize that the proportion of composite outcome responders will be significantly greater in the AD+EFAR arm than the single treatment arms.

Secondarily, pain+function responders will be significantly greater in the AD+EFAR arm compared to the other arms. Therefore 2 pairwise post-hoc comparisons will be made : (1) AD+EFAR vs. AD alone, and (2) AD+EFAR vs. EFAR alone. In our preliminary data from the 4-arm trial of AD and fear avoidance-based PT, the responder rate of pain+function in the AD+FABPT arm was 40%, the AD only arm was 20%, the FABPT only arm was 25%, and the Education only arm was 5%. In the Usual Care vs. EFAR comparison, EFAR had a 20% responder rate. We will assume that in the proposed study the rate of pain+function responders will be 20% in the AD or EFAR only groups, and 50% in the AD+EFAR group (since EFAR

appears to be an improvement over FABPT when multiple outcome domains are considered). For sufficient sample size to make inferences regarding the subcomponents of the primary composite measure (pain+function and depression), with equal sample size allocation amongst the 3 arms in the proposed study and using a two-sided significance level of 0.05, a sample size of 240 study completers (80 per arm) will provide about 95% power to detect a minimum difference of .30 from the baseline value of 0.20 in response rate for each hypothesis testing. After adjusting for a higher than anticipated drop-out and study withdrawal rate for the study at 4 months, the final sample size at enrollment will be about 330, *i.e.*, 110 per each arm.

Target enrollment is 330, if needed, and takes into account the higher than anticipated drop-out and study withdrawal rate for the study. Using our previous data, we anticipate that 30-35% of subjects will be prescribed opioids at the time of enrollment. Thus, we will enroll 195-205 nonopioid subjects and 95-105 opioid subjects. We are anticipating a 20% dropout rate in the nonopioid group and a 25% dropout rate in the opioid group over the four-month window to the primary endpoint. Thus, we anticipate 156 study completers in the nonopioid group and 84 completers in the opioid group. This totals to 240 participants needed to complete the study.

Hypothesis 1, Aim 1: The primary comparison of interest is the proportion of composite responders between study treatment arms at 4 months (nonopioid + opioid subjects together). A participant could be a pain+function responder, a depression responder, both, or neither.

For the sub-components of the composite outcome (pain+function) and depression responders in Hypothesis 1 in Aim 2, it is expected that depression changes will be more drastically different among the comparison arms since the depression response in the AD+FABPT arm was much greater than the pain+function response (a 75% rate of depression response), and the differences in depression response between arms was much greater in favor of AD+FABPT. Thus, the sample size estimated for the outcome of pain+function would be more than sufficient to maintain the same level of the powers.

Hypothesis 2, Aim 1: For the opioid misuse outcome in Hypothesis 2, Aim 2, power analyses are based on the incidence of a Drug Misuse Index (DMI) positive response at either 2 or 4 months, derived from our opioid misuse RCT. This study found that the control group with high NA ($n=25$) had a 75% rate of opioid misuse over 6 months and the intervention group with high NA receiving the psychosocial treatment had a 25% rate ($n=25$).¹⁴⁵ Based on enrollment data from the AD+FABPT pilot, we will assume that 35% of the recruited subjects will be prescribed opioids. With equal sample size allocation of 35:35:35 between any paired comparison opioid subgroups, we will have 85% power to detect a 30% absolute difference in the proportion of DMI-positive subjects, assuming (conservatively) that the rate of misuse in the AD and EFAR only groups is 60%, and the AD+EFAR group is 30%. For the reduced opioid dose outcome in Hypothesis 2, Aim 2, to identify a 60% reduction in dose in the AD+EFAR group vs. a 20% reduction in each other arm we will have about 80% power.

Hypothesis 3, Aim 2: We will create a patient-treatment matching prediction model. This will require an enriched pool of responders to the AD or EFAR only treatments since these response rates are lower than in AD+EFAR. The adaptive treatment strategy will generate 2 rounds of responders, those from the first randomization (AD, EFAR, or AD+EFAR) and those from the re-randomization of non-responders to AD or EFAR who will either continue the same treatment for 4 more months or switch to the other treatment. The first round of responders is anticipated to generate 50 AD+EFAR responders, 20 AD responders, and 20 EFAR responders, based on 100 enrolled subjects per arm. In the second round of responders due to the re-randomization, we anticipate 12 more AD and 12 more EFAR responders. This

is based on a 20% response rate each to the new AD or EFAR treatment and a 10% response rate each for the AD or EFAR subjects from the first randomization who continue the same treatment. It is possible that it could take more than 4 months to respond to the treatments and these subjects will be very informative to this issue. Thus, we anticipate having a total of 50 AD+EFAR, 32 AD, and 32 EFAR responder patients for analysis, vs. 186 non-responders (composed of study dropouts and actual non-responders to treatment). With the entire data set including both responders and non-responders, a logistic regression model will be used to build a prediction model including up to maximum 10 significant predictors via a variable selection method such as LASSO. The prediction error will be assessed and presented by using the Brier scores. It will be explored if the information of adaptive treatment could be utilized as an important predictor.

A cross-lagged panel analysis will be used to test if changes in conditioned pain modulation (CPM) precede changes in pain during the course of treatment in any of the treatment arms in either round of randomization. There are no sample size calculation formulas for cross-lagged panel analysis in the literature, and the analysis will be performed based on the sample size required for the primary hypothesis of Aim 2. Using guidance from previous pain studies performing this analysis, a sample size of 84 opioid subject completers (assuming a 20% dropout rate from the 105 enrolled) is within the range of successful cross-lagged panel analysis studies that examined if pain catastrophizing changes preceded pain changes, for example (N's=57-578).

Hypothesis 4, Aim 2: A mediation analysis is postulated to show that change in CPM is a mediator of changes in pain in the subjects prescribed opioids. We use the Vittinghoff approach to address the hypothesis that change in CPM will mediate the relationship between treatment (binary) and changes in pain. Mediation is the proportion of effect explained when adding the mediator to the model, after controlling for the primary predictor. We based our calculations on our previous CPM study in CLBP patients with high NA prescribed opioids and on the CPM data from the AD+FABPT pilot RCT. We estimate 84 total opioid subject completers (28 in each arm). Assuming change in centered CPM (mediator) and treatment (primary predictor) have a correlation coefficient of 0.5, and the regression coefficient for the mediator is $\log(1.67)$ and the regression coefficient for the binary treatment variable is $\log(2)$, a sample size of 84 subjects for each pairwise comparison would have 80% power at a two-sided 5% significance level to detect the mediation effect of 30%, *i.e.* the proportion of treatment effect explained due to the mediator.

Exploratory Aims: Although sample size calculations for qualitative research cannot be calculated a priori as they are contingent on evolving theoretical categories, little new information is generated after interviewing 20 people belonging to a relevant participant 'category' and no more than 50-60 total interviews are recommended. Thus, we will conduct qualitative interviews with 60 participants, 20 from each of the three sites, for a total of 60 qualitative interviews allowing for content saturation.

9.3 POPULATIONS FOR ANALYSES

N/A

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Dr. Ma will oversee data analyses. We will evaluate the statistical properties of baseline and follow-up

outcome measures, including potential outliers, normality, and missing data. We will compute measures of central tendency (means, medians, other percentiles) and dispersion (standard deviations, ranges) for continuous variables, whereas we will calculate frequency distributions for categorical data. We will compare distributions of baseline characteristics between groups to assess effectiveness of randomization, and we will adjust for statistical or clinical differences in secondary analyses.

Aim 1, Hypothesis 1: The two-sided Z-Test for the proportions with unpooled variance will be used to compare the response rates. Logistic regression models will be used to estimate the response rates, adjusting for confounding factors. Analysis will be done on 2, 4, and 8 months timepoint data. The linear mixed model will be utilized if the intervention arms were to be compared using the longitudinal data of pain scores, depression, and function. This technique has advantages in handling missing data and analyzing covariates/ confounders for repeated measures data. Regarding the evaluation of concurrent opioid use as a moderator of treatment effects, interaction of opioid use and treatment groups will be tested for each pairwise comparison in the logistic regression models.

Subjects with missing data will be included in the data analysis, following a modified principle of intention-to-treat analysis, provided that the patients had treatment exposure. We will analyze the secondary outcomes in the same manner.

Aim 1, Hypothesis 2: To investigate if improved negative affect (NA) will result in less opioid misuse, we will compare DMI-positive responses between the 3 arms using an extension of Fisher's Exact test, described by Freeman and Halton. We will use logistic regression analyses to test any differences between groups, controlling for potential confounders, such as: DMI at baseline, other measures imbalanced at baseline (*e.g.*, duration and severity of symptoms, radicular pain, medical comorbidities) and other biological variables (gender, race, and ethnicity). We will use the same approach to compare differences in opioid dose reductions between groups.

Aim 2, Hypothesis 3: Even if the combined treatment turns out to be more effective than mono-therapy it might not be clear if each mono-therapy contributes unique effects in relation to patient symptoms. For example, more serious depression might predict a better response to AD, and more anxiety (especially anxiety about movement), might predict a better response to EFAR. Those with disproportionately worse function may also respond better to EFAR, for instance. A patient-treatment matching prediction model will be developed using the entire data set to identify possible predictors of treatment responses in each intervention group. The treatment group indicator will be included as the primary predictor in the logistic regression, together with other risk factors, which will be categorized into low-, mid-, and high-risk groups. The final model will predict the treatment response probability among subjects from each intervention arm at different risk levels, and its prediction ability will be evaluated by using the Brier scores.

Aim 2, Hypothesis 4: A cross-lagged panel analysis will be conducted to determine the temporal associations between CPM and pain, based on the available sample size required for the primary hypothesis of Aim 2. We will follow analysis plans described in the pain literature. Any missing data at 2-month or 4-month follow-up can be imputed using multiple imputation technique. We plan to first explore the associations using change scores. The zero-order Pearson correlations will be calculated to assess the association between CPM and pain on changes from baseline to 2-month follow-up, and from 2-month to 4-month follow-up. Additionally, a repeated-measures analysis of variance on change scores will be used to determine whether the variables improve significantly from baseline to 2-month follow-up, from 2-month to 4-month follow-up, and from baseline to 4-month follow-up. To avoid the potential dependence between baseline scores and change scores, standardized residualized change scores will be used to perform the cross-lagged analysis. Similar zero-order Pearson correlations will be examined on the residualized changes. Lastly, linear regression analyses using the residualized changes will be

conducted to evaluate whether baseline to 4-month CPM accounted for unique variances in 2-month to 4-month pain, and vice versa. To control for potential confounders, the analyses account for two extraneous sources of variance: (1) autocorrelation, which is the correlation of the same variable at different time points, and (2) synchronous correlation, which is the correlation between different variables at the same time point.

For the mediation hypothesis (Aim 2, Hypothesis 4) regarding CPM mediating treatment responses, the outcomes of pain, function, depression, anxiety, and CPM are continuous. We will use the Baron and Kenny criteria to establish mediation through the linear regressions, with bootstrapping for calculating indirect effects, confidence intervals, and significance testing. The Sobel test will be used to test the significance of a mediation effect. We will investigate potential confounding using the multivariate techniques as described by Dunn and Bentall. We recognize that CPM may end up being a moderator instead of a mediator of outcomes in the final analysis.

To examine IHRS as a potential treatment moderator, we will first create a composite categorical variable representing IHRS (46). To do so, we will first complete a median split for each type of internalized stigma (i.e., mental health, pain, and opioid use). Then those above the medians for all three types of stigma will be identified as “high” IHRS. Those below the median for all types of stigma will be identified as “low” IHRS. Those above the median in only one type of stigma will be identified as “mild” and those above the median for two types of stigma will be identified as “moderate”. We will employ the PROCESS macro to examine the potential moderating effect of IHRS on treatment outcomes. This program examines the conditional effects of the independent variable (treatment type) on the dependent variable (treatment outcome) at each level of the moderator (IHRS). We will create three separate models, one for each of the three outcomes of interest (pain severity, physical function, and depression).

To examine the impact of EFAR on IHRS, we employ three separate repeated-measures analyses of covariance (ANCOVA), one for each outcome of interest (i.e., mental health, pain-, and opioid-related stigma). All participants randomized to EFAR or EFAR + AD will be included in these analyses.

To analyze qualitative interview data, we will use thematic analysis. Initial ideas will be identified and coded using inductive and deductive processes to identify emerging themes. We will explore and analyze the attitudes, understanding, and needs of interviewees such that this data will drive intervention development. This will allow us to include components that seem most acceptable, feasible, and salient while avoiding components that seem impractical or intrusive.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

This is described in sections 9.2-9.4.1 above.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For each secondary endpoint:

This is described in sections 9.2-9.4.1 above.

9.4.4 SAFETY ANALYSES

N/A. We are not testing the efficacy of the antidepressant medication used in this study which is already FDA approved. We will track side effects and AEs and report their rates.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Intervention groups will be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics.

9.4.6 PLANNED INTERIM ANALYSES

There is no planned interim analysis of the aggregate participant data. At the end of the four-month treatment blocks each subject has the primary endpoint calculated for responder/non-responder for change in pain+function and depression. This is done so that non-responders in the AD or EFAR only arms can be rerandomized.

9.4.7 SUB-GROUP ANALYSES

This is described in sections 9.2-9.4.1 above. We will conduct subgroup analyses based on age, sex, and race/ethnicity for all endpoints. In addition, these factors are considered in the logistic regression models for determining predictors of treatment responses.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

As noted, at the end of each four-month treatment phase we do tabulate responder/nonresponder metrics for pain+function and depression.

9.4.9 EXPLORATORY ANALYSES

This is described in sections 9.2-9.4.1 above.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

The study informed consent process will be administered by the study coordinator or study team staff during Study Visit 1 before any study procedures begin. The study coordinator will explain risks and benefits, reminding participants that their participation is voluntary and can choose to withdraw at any time. Any potential costs and protection of health information will also be discussed. Additionally, contact information in case of medical emergency due to participation, or questions about subject rights will be provided and emphasized during the consent process. Once the participant has signed the consent form, a copy of the consent form will be provided to the participant. The signed copy will be placed in his/her study file locked in a designated study cabinet.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant during Study Visit 1 and written documentation of informed consent is required prior to starting intervention/administering study intervention. A copy of the consent form will be handed to the participants for them to review as needed. There are no additional informational documents provided to participants.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document.

The study coordinator will be administering the consent process and will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing, as well as have the opportunity for the study coordinator to review the consent form together. The participants will have the opportunity to discuss the study with their family and think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study during Study Visit 1. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The rights and welfare of the participants will be protected by highlighting to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. There will be no effects on their current or future relationship with the institution, their current or future medical care at UPMC hospital, Brigham and Women's hospital, and Mayo Clinic, or their current or future relationship with a healthcare insurance provider based on their decision of participation. A copy of the informed consent document will be given to the participants for their records after they have signed the consent form. The informed consent process will be conducted and documented in the Study Checklist document (including the date), and the form signed, before the participant undergoes any study-specific procedures.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, and NIAMS. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the local Institutional Review Boards (IRBs), central IRB, and NIAMS and will provide the reason for the termination or suspension. Study participants will be contacted, as needed, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Study closure based on PI or NIAMS decision

- Determination of unexpected, significant, or unacceptable risk to participants (based on AEs, SAEs, protocol deviation/violation, and unanticipated problems reporting)
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the NIAMS and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their study staff, and the NIAMS. This confidentiality is extended to cover testing of biological samples (e.g. urine toxicology test) in addition to the medical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in private setting designated for research purposes. Data identifying participants that are stored electronically will be maintained in a secured study folder. Each site has a designated location to store electronic study files. Access to this folder will be granted by the site investigators to the study team and authorized personnel associated with the study. Paper forms or pages containing personal identifying information will be kept in a safe and locked cabinet accessible to only the research team. All research documents will be linked to the participant's unique study ID. Subject anonymity will be preserved by the use of a unique subject ID such as TNA-001.

The study monitor, NIAMS, representatives of the Institutional Review Board (IRB), or pharmaceutical company supplying antidepressant medication may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

This research study will involve the recording of past, current and/or future identifiable medical information from participant's hospital and/or other health care provider (e.g. physician office). The information that will be recorded will be limited to diagnostic information, lab results, medications, demographics, and medical history. The information will be used to determine participant eligibility for this study and to follow their care once they are enrolled in the study. In addition to the investigators, the research staff, and NIAMS, the following individuals will or may have access to identifiable information related to your participation in this research study:

- Authorized representatives of the University of Pittsburgh Office of Research Protections may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.
- Authorized representatives of the UPMC, BWH, or Mayo Clinic hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2)

addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

- Individuals from the National Institutes of Health and the Food and Drug Administration will be able to access research data, including your private health information for purposes of monitoring the research. Although these organizations have safeguards to protect your privacy, we cannot guarantee the confidentiality of your health information after it has been obtained by those organizations.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure file cabinet accessible only to study team members and authorized personnel for at least 7 years as indicated by the reviewing IRB.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Pittsburgh Data Coordinating Center (DCC). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. Data listings that contain participant name, initials, or other identifiers easily associated with a specific participant will not be distributed. The study data entry and study management systems used by clinical sites and by the University of Pittsburgh DCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the DCC.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of Pittsburgh. After the study is completed, the de-identified, archived data will be transmitted to and stored at the BACPAC data repository for use by other researchers including those outside of the study. Permission to transmit data to BACPAC data repository will be included in the informed consent.

Urine samples collected for the urine toxicology drug test are analyzed by an outside 3rd party vendor. They will NOT be stored. The test will be administered by the study coordinator and will be identified using the participant's unique study ID. There are no plans to maintain the sample for future use or studies.

When the study is completed, access to study data will be provided through the BACPAC data repository.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including but not limited to pain psychology, clinical psychology, and bioethics. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. Ongoing responsibilities of the DSMB are to evaluate the progress of intervention trials, review study performance, ensure protections are in place for the safety and privacy of study participants, and consider the impact of factors external to the study when new, related information becomes available. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB is advisory to the NIAMS and will provide its input to the NIAMS.

The frequency of data review for this study differs according to the type of data. Subject accrual including compliance with protocol enrollment criteria will be reviewed weekly and bi-annually. Status of all enrolled subjects, adherence data, and Adverse Events will be disclosed and discussed with DSMB monthly and bi-annually. Serious Adverse Events reporting will be reported to the DSMB per occurrence. Further details about the frequency of reporting to DSMB will be included in **Section 3.1, Frequency of Data and Safety Monitoring** on the Data and Safety Monitoring Plan (DSMB).

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirements from IRB.

- The site PIs and/or project managers will conduct the on-site monitoring once a year to review written Standard Operating Procedures (SOPs) and data acquisition quality.
- Independent audits will be conducted by the site-PIs or project managers to ensure monitoring practices are performed consistently across all participating sites. However, site PIs and project managers will be available resources throughout the study period to answer any questions that the study team members may have.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the study coordinator or designated study staff at the study site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCap system, a 21 CFR Part 11-compliant data capture system provided by the University of Pittsburgh IRB. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

The following documents and measures are utilized in the study:

- Informed Consent
- Demographics
- Medical History
- Urine Drug Toxicology Test (screening purposes)
- Urine Pregnancy Test (screening purposes)
- QST in excel format
- Antidepressant Treatment History Form
- Self-Administered Co-Morbidity Questionnaire
- BACPAC Minimum Dataset
- Addiction Behavior Checklist (ABC)
- Drug Misuse Index
- Current Opioid Misuse Measure (COMM)
- Opioid Side Effect Checklist

- Opioid Craving Questions
- Medication Log
- Widespread Pain Index + Symptom Severity
- Pain Self-Management Log
- PainDETECT
- PROPr
- PROMIS Pain Behavior
- Fear Avoidance Beliefs Questionnaire (FABQ-PA)
- Pain Catastrophizing Scale
- Columbia-Suicide Severity Rating Scale (CSSRS)
- Pre-Treatment Assessment
- Treatment Helpfulness Questionnaire
- Patient Global Impression of Change (PGIC)
- PHQ-4
- PHQ-9
- FIBSER
- AD Side Effects Checklist
- Fear of Daily Activities Questionnaire (FDAQ)

All study measures are collected electronically with the exception of these following measures/documents on paper. This will also serve as the source documentation: Informed consent form, Medical History form, Antidepressant Treatment History form, Addiction Behaviors Checklist, Drug Misuse Index, Urine Drug Toxicology Requisition Forms, and Columbia-Suicide Severity Rating Scale.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a period of three years from the date of Federal Financial Report (FFR) submission, per NIH guidelines. These research documents will be retained for a longer period, however, required by local IRB regulations. After the study ends, all research records and participant forms will be maintained in a secure location for 7 years following final reporting or publication of a project. Permission by NIAMS is not required prior to destruction of records.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation or violation is a departure from the IRB-approved protocol. Such departures may be minor or major depending on the situation. The departure may be either on the part of the investigator, or the study site staff and should be refrained. Examples of protocol deviation or violation may include unreported SAEs, incorrect or missing study measures (not collected by study staff), and study visits occurring outside of the specified time frame. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report major deviations 5 working days of identification of the protocol deviation to the local Institutional Review Board (IRB) per their policies. Minor deviations will be reported annually to the NIAMS, DSMB, local IRB,

and central IRB at University of Pittsburgh. All deviations must be addressed in study source documents, reported to NIAMS and DSMB. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in **Section 15.0, Study Compliance** on the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](#) upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Data from this study will be made available as a limited data set through a data use agreement after acceptance for publication of the main findings of the final data set. All shared data will be de-identified; Protected health information (PHI) will be removed in compliance with the HIPAA Privacy Rule. Data, such as hospital admission, discharge, and surgical dates, may be altered to protect patient privacy, but will not affect statistical analyses. A data-use sharing agreement between University of Pittsburgh and the individual or institution requesting the dataset will be required. This agreement will stipulate the individual or institution will maintain the privacy and confidentiality of data and that data will not be re-disclosed to outside sources. The requestor must also indicate how data is stored to demonstrate compliance with secure computing, and must provide a letter from the IRB approving use of the data for research purposes and security plans.

This proposal will adhere to NIH Grants Policy on Availability of Research Results: Publications, Intellectual Property Rights, and Sharing Biomedical Research Resources. Specifically, transfers of research materials out of the laboratory to other researchers will be made under terms no more restrictive than in the Simple Letter Agreement for the Transfer of Materials or the Uniform Biological Materials Transfer Agreement (UBMTA), and made without reach-through requirements. Should any intellectual property arise that may be patentable, we will ensure that the related materials and final research data remain widely available in a timely fashion to the research community in compliance with policies and regulations governing research awards from the NIH. As the studies mature, reprints and abstracts of the studies will be made available on the Center's website. Access to the data would follow a review of any relevant IRB and HIPAA issues that apply to the transfer of research data on human subjects.

10.1.12 CONFLICT OF INTEREST POLICY

Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIAMS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. All study members must comply with the policies governing activity. If it is determined, after disclosure, that a conflict exists, NIAMS may decide whether the conflict must be eliminated or can be managed.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

AE	Adverse Event
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
MOP	Manual of Procedures
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
SAE	Serious Adverse Event
SOA	Schedule of Activities
UP	Unanticipated Problem
US	United States

11 REFERENCES

Provided is a list of relevant literature to protocol and citations of publications reference in the text of the protocol:

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