Official Title: Pain Response Evaluation of a Combined Intervention to Cope Effectively
NCT04395001
IRB Approval Date: 10/21/2022

Pain Response Evaluation of a Combined Intervention to Cope Effectively (PRECICE)

Protocol Number*: 1

National Clinical Trial (NCT) Identified Number: NCT04395001

Principal Investigator*: Dennis C Ang, MD

Sponsor: Wake Forest Health Sciences (WFHS)

Grant Title: Pain Response Evaluation of a Combined Intervention to Cope Effectively (PRECICE)

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Statement of Changes:

See Section 10.4, Protocol Amendment History, for a list of changes.

CONFIDENTIALITY STATEMENT

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STATEMENT OF COMPLIANCE

PRECICE will be carried out in accordance with International Council 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).

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 IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) 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.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name*: Dennis C. Ang, MD, MS

Title*: Principal Investigator (PI), Chief of Rheumatology and Immunology

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Pain Response Evaluation of a Combined Intervention to Cope Effectively (PRECICE)

Grant Number: 1UG3NR019196-01

Study Description: The purpose of this research is to determine if the combination of non-opioid medication (duloxetine) and web-based pain-coping skills training (PCST), with or without health care professional support, is beneficial for individuals with chronic musculoskeletal pain (CMP).

Objectives*: The objective of this study is to conduct a 24-week randomized clinical trial of primary care patients with CMP. 280 participants will be randomized to one of three treatments: (1) combination treatment [duloxetine + web-based cognitive behavioral therapy CBT] with health care professional support, (2) combination treatment without health care professional support, and (3) duloxetine monotherapy.

Endpoints*: Primary Endpoint: Brief Pain Inventory (BPI)-Global Pain Severity (GPS)

Subgroup Analyses: We will conduct subgroup analysis using linear mixed effects models (LMMs) to test the interactions between intervention arm (with and without health care professional support vs. monotherapy) and baseline characteristics.

Secondary Endpoints:
The secondary outcomes will include the two individual components of the BPI GPS: BPI pain severity and BPI pain interference.

Tertiary Endpoints:
1. *Global Rating of Change (GRC)*
2. PROMIS pain intensity
3. PROMIS pain interference
4. Chronic Pain Coping Inventory (CPCI)

Exploratory Endpoints:
1. *Generalized Anxiety Disorder 7-item scale (GAD-7)*
2. *Patient Health Questionnaire 8-Item Depression Scale (*PHQ-8)
3. Pain catastrophizing scale (PCS)
4. ~~SF-36 physical function (SF-36)~~
4. PROMIS Adult measures: physical function, fatigue, social health, sleep disturbance, pain behavior
5. *Opioid Morphine Equivalent (OME)*
6. Health care service utilization
7. *PHQ Anxiety-Depression Scale (PHQ-ADS)*
8. *Frequency of Practicing Pain Coping Skills*
9. *Others.* Medication use and co-intervention effect.

For a full description of these endpoints see section 8.1.

Study Population:	(1) patients at the primary care clinic with daily pain for 3 months or longer affecting the low back, neck, hip, knee or widespread pain; 2) at least moderate in BPI GPS, defined as a GPS score of 5 or greater[1,2]; and (3) at least age 18 years old or older. ~~We are restricting our age criteria because of the risk of poly-pharmacy from centrally-acting medications in older adults.~~ All sexes who meet these criteria are eligible for the study. (n=280)
Phase* or Stage:	Phase 4
Description of Sites/Facilities Enrolling Participants:	We will recruit participants from the 271 primary care clinics within the Atrium Health - Wake Forest (WF) Baptist Health System as well as surrounding providers outside of Atrium Health in North Carolina .

Description of Study Intervention/Experimental Manipulation:

PRECICE is a 24-week randomized controlled clinical trial (RCT) of patients in the primary care clinics. During the study, participants will be randomized to one of three treatments: (1) [duloxetine + web-based CBT] with health care professional support, **vs**. (2) [duloxetine + web-based CBT] without health care professional support, **vs.** (3) duloxetine only.

Web-based Cognitive Behavioral Therapy (web-based CBT). The web-based CBT program is an automated program (i.e., users learn skills with interactive, personalized training without any therapist contact) that includes 8, 35- to 45-minute training sessions, each of which provides an educational rationale and training in cognitive or behavioral pain coping skill drawn from face-to-face CBT [3].

Health care professional-delivered Motivational Interviewing (MI). The primary purpose of health care professional contact is to enhance participant's motivation to engage in web-based CBT by encouraging participant's continued use and practice of pain coping skills. Subjects randomized to the [duloxetine + web-based CBT] with health care professional support will receive 6 phone calls from a MI trained health care professional at week 3, 6, 10, 14, 18 and 22. Telephone sessions may run for 20 minutes on the average.

Duloxetine. We chose duloxetine as the first line drug because: (1) it has established efficacy for CMP and Food and Drug Administration (FDA) approval for that indication; and (2) it is available in generic form, which makes it more readily available. At study entry, all participants will receive duloxetine 30 mg once daily for one week; subjects who are able to tolerate 30 mg and do not have chronic kidney disease III (CKD-3) will increase to 60 mg once daily for 24 weeks. At week 25, participants will return to the research clinic for outcome assessments. At the last study visit (week 25), participants who would like to stop the medication, will be provided duloxetine 30 mg once daily for 7 days and medication treatment will then stop (tapering regimen). Subjects already taking 30 mg daily will stop dosing at their week 25 visit. Those who would like to continue duloxetine will be prescribed a 2-week supply of duloxetine and will be instructed to talk to their primary care provider (PCP). In addition, the investigator will send a Wake One message to the PCP to consider continuation of duloxetine.

Other treatments. The use of over-the-counter analgesic medications will be permitted and assessed to adjust for co-intervention differences between groups in the analyses.

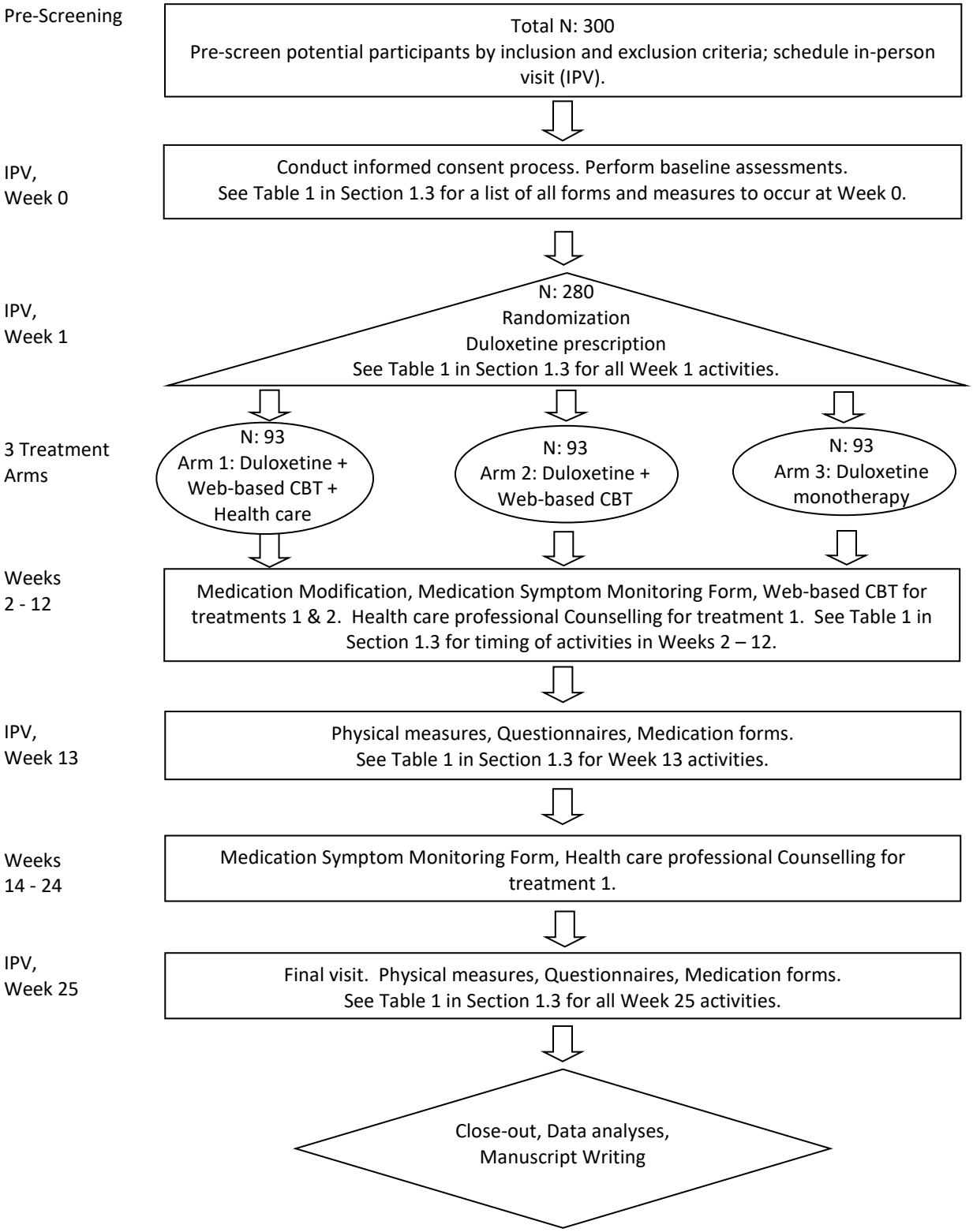
For further details, see Section 6, Study Interventions or Experimental Manipulations.

Study Duration*: The estimated time from when the study opens to enrollment until completion of data collection is 45 months.

Participant Duration: The time it will take for each individual participant to complete all study-related tasks is 25 weeks.

1.2 SCHEMA

Flow Diagram



1.3 SCHEDULE OF ACTIVITIES

Table 1. Study Measures and Time Points for Data Collection in PRECICE

Telephone Contacts/Visits [a]	Pre-Screening Visit	Week 0	Week 1	Week 2	Week 3	Week 4	Week 6	Week 10	Week 13	Week 14	Week 18	Week 22	Week 25	PRN
Type of Contact/Visit [b,c]	TC	IPV	IPV	TC	TC	TC	TC	TC	IPV	TC	TC	TC	IPV	PRN
Screening														
Phone Pre-Screening	✔													
Randomization			✔											
Physical Measures														
Blood Pressure		✔	✔						✔				✔	
Height		✔												
Weight		✔											✔	
Urine Pregnancy Test		✔							✔					
Questionnaires														
3-item Pain Intensity Interview		✔							✔				✔	
Compiled Questionnaires ○ Brief Pain Inventory ○ Generalized Anxiety Disorder (GAD-7) ○ Patient Health Questionnaire (PHQ8) ○ Global Rating of Change (GRoC) ○ Pain Catastrophizing Scale (PCS) ○ PROMIS Adult Self-Report ○ Chronic Pain Coping Inventory (CPCI)		✔							✔				✔	
Demographics with Medical Diagnosis		✔												
Informed Consent		✔												
Missed Visit Form														✔
Modified Pain Detect		✔												
Non-study Medication List		✔							✔				✔	
Nurse Counselling Tracking Form					✔		✔	✔		✔	✔	✔		
Opioid Risk Tool		✔												
Participant Status														✔
Serious Adverse Event Report Form														✔
Study Drug Accountability Log		✔ [d]	✔ [e]						✔				✔ [f]	
Study Medication Modification				✔					✔				✔	✔ [g]
Study Medication Symptom Monitoring Form			✔	✔ [i]		✔ [i]			✔				✔	✔
TAPS – Tobacco, Alcohol, Prescription		✔												
EMR Health Care Utilization [h]														

[a] Weeks with participant contact are listed on this table.
[b] IPV indicates in-person visit.
[c] TC indicates telephone contact.
[d] At study entry, all participants will receive duloxetine 30 mg once daily for one week.
[e] At week 1, participants will receive duloxetine 60 mg once daily for 24 weeks.
[f] At week 25, all participants will be provided duloxetine 30 mg once daily for 7 days and medication treatment will then stop (tapering regimen).
[g] Phone administration on as needed basis only if participant calls the research office and complains of a potential side effect.
[h] EMR Health Care Utilization will be collected at one year after randomization.
[i] Option of using text messaging as an adjunct to phone calls to assess duloxetine symptoms monitoring at weeks 2 and 4.

Revised 07/19/2021

2 INTRODUCTION

2.1 STUDY RATIONALE

Significance

With our proposed work, we hope to address two important unanswered questions: (1) Does combination treatment consisting of duloxetine and web-based CBT optimize treatment outcomes? (2) Would adherence-focused guidance delivered by health care professional clinician using MI techniques enhance treatment effectiveness? Our proposed work is significant because we aim to optimize pain-related treatment outcomes at the primary care level where most patients with pain are managed. Importantly, the use of health care professional clinician providing adherence-focused guidance (as opposed to content-focused guidance) on the continued practice (or use) of pain coping skills increases the likelihood that our proposed intervention is scalable in the future. Effective, accessible and scalable psychoeducational treatments are needed to manage CMP in real world clinic settings [4].

Objectives

The **objective** of this UH3 application is to conduct a 24-week randomized clinical trial of primary care patients with CMP. In the UH3 trial, 280 participants will be randomized to one of three treatments: (1)

combination treatment [duloxetine + web-based CBT] with health care professional support, (2) combination treatment without health care professional support, and (3) duloxetine monotherapy.

Specific Aim 1. To compare combination treatment (with and without health care professional support) and duloxetine monotherapy in improving GPS (as measured by BPI pain severity and interference).
H1: Combination treatment with and without health care professional support is more effective than duloxetine monotherapy in improving GPS.

Specific Aim 2. To examine if health care professional support to increase participants' motivation on continued practice of pain coping skills will enhance treatment outcomes among those who receive combination treatment.
H2: Combination treatment with health care professional support is more effective than combination treatment without health care professional support in improving GPS.

2.2 BACKGROUND

Abnormal Endogenous Pain Modulation: Shared Biology among CMP Conditions

A major problem in designing new therapies to treat CMP is that the underlying mechanisms driving musculoskeletal pain are not fully understood [5,6]. In fact, physical findings in patients with CMP are poor predictors for self-reported pain severity and dysfunction [7]. Moreover, the extent of tissue abnormalities appears to be poorly correlated with self-reported pain intensity [8]. For example, minor radiographic abnormalities of the spine or knee may be painless in some individuals but may be associated with severe chronic pain in others [9]. The poor correlation of patients' peripheral tissue abnormalities with chronic pain intensity has shifted research to focus on central pain processing abnormalities as the primary causal factors of chronic pain [10]. Augmented central nervous system (CNS) processing of nociceptive signals and dysfunctional endogenous pain inhibition have been identified as characteristics of many musculoskeletal pain conditions [7,10-12] including low back pain, neck pain, temporomandibular disorder (TMD), osteoarthritis, and fibromyalgia [13-18].

Duloxetine: Efficacious in CMP Conditions

Augmented CNS processing of nociceptive signals and dysfunctional endogenous pain inhibition contribute to central sensitization. Central sensitization manifests as pain hypersensitivity, particularly tactile allodynia (painful response to a normally innocuous touch), pressure hyperalgesia, and enhanced temporal summation [19]. In preclinical studies of pain, duloxetine, a selective serotonin norepinephrine reuptake inhibitor, reduces central sensitization [20-22]. In clinical studies, the efficacy of duloxetine is well documented in many of the musculoskeletal pain conditions including fibromyalgia [23,24], osteoarthritis, and chronic low back pain [25].

Psychological Factors in Chronic Pain

Two key factors that have important clinical implications for pain management are pain-related appraisals and beliefs (including catastrophizing), and pain coping [26].
Pain-related appraisals and beliefs about pain can affect an individual's affective and behavioral response to pain[27,28]. People are less able to adjust to pain when they believe that pain is a signal of damage, activity should be avoided when one has pain, pain leads to disability, pain is uncontrollable, and pain is a permanent condition [27,29]. For example, patients with low back pain believed that a wrong movement could have serious negative consequences for their back [2]. Moreover, this belief was

associated with reduced activity levels and increased disability. Among patients with fibromyalgia, positive outcomes were most closely related to: (1) an increased sense of control over pain, (2) a belief that one is not necessarily disabled by pain, and (3) a belief that pain is not necessarily a sign of damage [30].

One pain-related appraisal, catastrophizing (defined as an exaggerated negative orientation toward actual or anticipated pain experience and effects), has been an important therapeutic target in managing chronic pain [31-33].

***Pain coping*.** Coping is the use of behavioral and cognitive techniques to manage demands perceived as stressful [34]. Variations in pain coping are significantly related to pain, physical function and pain behavior [35-37]. Both active and passive coping dimensions are significantly related to chronic pain adjustment [38]. In patients with osteoarthritis, greater self-control and increased rational thinking were associated with lower pain ratings and less self-reported physical disability [39]. Among chronic pain patients, both poor coping skills and maladaptive pain related beliefs predicted physical disability[27]. These findings suggest the importance of targeting specific pain-related beliefs and coping strategies for modification to reduce physical disability.

Cognitive Behavioral Therapy (CBT)

Modification of cognition (pain-related appraisals and beliefs) and behavior can positively or negatively affect the course of an individual's chronic pain condition. The goal of CBT is to aid the patient in re-conceptualizing his or her personal view of pain and role (from passive to a more proactive role) in the process of healing. CBT is effective in the management of low back pain, neck pain, temporomandibular joint pain, knee osteoarthritis, and fibromyalgia [40].

Scientific Premise

i. Optimizing Treatment Outcome: Combining Duloxetine and CBT

The bio-psychosocial model is particularly useful for understanding chronic painful conditions even when etiologies are vague [41,42]. This model suggests that coping with illness involves a complex interaction of biological factors (central sensitization), psychological factors (mood and thoughts) and the social context (interpersonal relationships) [43]. Along with drug management, a treatment approach based on the bio-psychosocial model involves addressing the psychosocial issues relevant to chronic pain. Unfortunately, only a few trials have tested medications plus non-pharmacologic treatments. In migraine headaches, the combination of beta blockers and behavioral migraine management was more effective than either therapy alone in reducing headache severity [44]. In chronic tension headaches, tricyclic antidepressant plus stress management notably reduced the severity of headaches over 1 month, compared to either intervention alone [45]. In non-cardiac chest pain, the combination of pain coping skills training and sertraline significantly reduced pain intensity and pain unpleasantness [46]. In CMP, a collaborative care team approach that delivered multi-component treatment program (medication and pain self-management training) improved pain-related outcomes compared to usual care [47].

Preliminary Data: In our feasibility study [48], 58 patients with chronic widespread pain (fibromyalgia) were randomized to: (1) combination milnacipran (100 mg/day) + CBT (n=20), (2) milnacipran (100 mg/day) + education control (n=19), or (3) placebo medication + CBT (n=19). Participants received

either milnacipran (100 mg/day) or placebo. They also received 8 sessions of phone-delivered CBT or educational instructions. One of the primary endpoints was a composite responder rate; responders were defined as participants who reported a ≥30% reduction from baseline in the weekly average pain severity, and ≥10-point improvement from baseline in the SF-36 physical function score. We found a 41% composite responder rate for combination treatment versus 24% for milnacipran and 7% for CBT. We concluded that a therapeutic approach that combines CBT and milnacipran (*a medication closely related to duloxetine*) was feasible and acceptable [48]. The observed effect sizes indicated that a full clinical trial was warranted.

While the reasons why medicine has not moved beyond the biomedical model are complex (e.g., inadequate economic incentives, continued focus on biomedical models in medical school education), the scarcity of comparative effectiveness studies to support the use of the bio-psychosocial model in CMP is another important factor.

ii. Web-based CBT to Improve Access

Despite the proven efficacy of traditional face-to-face CBT [49], access to care is one major limitation. Barriers to accessing face-to-face programs are numerous and include cost, stigma, and availability of psychologists that are trained in pain management. Consequently, the use of CBT in primary care where most patients with CMP are seen, is rare.

Web-delivered CBT is one innovative approach to increase access to pain management programs. Web-based programs use the same principles, content, and components as face-to-face programs but can be provided with varying levels of clinician support ranging from regular clinician contact to no clinician support at all.

Systematic reviews have reported *small but clinically significant* improvements in pain severity (effect size/ES= 0.33) and disability (ES= 0.39) [50,51].

iii. Importance of Maintaining and Enhancing Treatment Outcome of Web-based CBT

As in the in-person CBT protocol, participants in a web-based CBT program are typically asked to practice each new cognitive or behavioral pain coping skill after learning it. Fundamental to the long term effectiveness of CBT is the requirement that pain coping skills are applied or practiced on a regular basis. In a study of traditional CBT for chronic pain, pre- to post-treatment changes in pain control and catastrophizing mediated the effects of CBT on pain and activity interference[52]. In fibromyalgia, treatment outcomes were most closely related to 5 coping strategies or skills: decreased guarding, increased use of exercise, seeking support from others, activity pacing, and use of coping self-statements [30]. Unfortunately, as with face-to-face CBT programs, maintenance of clinical improvements from web-based CBT has **not** been consistently observed [50] partly due to reduced use of cognitive and behavioral pain coping skills over time.

Rini C, Keefe F et al. evaluated the effectiveness of web-based CBT (**+** physiotherapist-guided home exercise delivered through Skype) to 148 persons with chronic knee pain. Improvements in pain and function with the intervention were large at 3 months (immediate post-intervention) and were greater than those in the control group[3]. Benefits were apparent at follow-up, although between group differences were reduced. Further, 64% of the CBT practice exercises (i.e., relaxation, coping thoughts, pleasant imagery, distraction, problem solving, activity-rest cycling, pleasant activity

scheduling) were completed at 3 months with numbers decreasing during follow-up to 41%. Based on these findings, treatment strategies are needed to motivate continuous use or practice of pain coping skills to achieve long term success.

iv. MI to Enhance Benefits of Web-based CBT

MI is an effective counseling approach to elicit behavior change (e.g., from sedentary lifestyle to physically active lifestyle, from poor food choices to healthier food choices to achieve weight loss, etc.) [53-57]. In contrast to delivering simple advice, a MI-trained health care professional helps a patient discuss the pros and cons, and the barriers and solutions to behavior change; consequently, enhancing self-efficacy. Self-efficacy determines whether an individual attempts a given task, the degree of persistence when difficulty is encountered and ultimate success or failure of the behavior.

Preliminary Data: In our RCT study [58], 216 participants with fibromyalgia were randomized to MI to increase physical activity vs. education (attention) control. Over a 12-week period, participants received either **six** telephone-delivered MI or educational (attention control) instructions. Post intervention, MI was superior to control in increasing the number of weekly hours of self-report physical activity. At follow up, more MI participants than controls exhibited meaningful improvement in global severity. Additionally, participants in the MI group had a significantly greater improvement (i.e., walked longer distance) in the 6-minute walk test compared to controls.

Given our success on the use of telephone-delivered MI, it is reasonable to hypothesize that six sessions of telephone-delivered MI to increase participant's continued practice of pain coping skills will enhance treatment outcomes.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks primarily involve direct adverse effects of duloxetine which are well-described and minimal (i.e., sedation, nausea, headache, and dizziness that are typically transient in nature) in most individuals. For those who do not tolerate the side effects, the medication will be reduced or discontinued with an appropriate 7-day tapering regimen to prevent discontinuation syndrome. Side effects of these medications resolve shortly after stopping them.

Pregnant women are excluded from participation in this study. Because NO method of birth control is 100% reliable, a pregnancy test is required at baseline and at week 13. For subjects who become pregnant while in the study, duloxetine will be discontinued (with appropriate tapering regimen), and subjects will be allowed to continue with the study.

If a participant happens to become pregnant while in the study, the **rare** side effects of duloxetine for the fetus late in the third trimester include breathing difficulties, seizures, temperature instability, feeding difficulty, vomiting, low blood sugar, jitteriness, irritability, and tremor. To avoid unnecessary exposure to duloxetine, participants will get a repeat urine pregnancy test mid-way (week 13) during the 24 week study period. The enumerated side effects are side effects for the newborn.

Other potential risks include emotional distress related to the web-based pain coping skills training, which is typically a minor issue. Our trained research assistant, who collects information on medication

side effects, will be able to ask about emotional distress, with an agreed upon approach to refer participants to the medical safety officer if any concerns are present. Participants should discuss the risk of being in this study with the study staff.

There are no additional tests performed while enrolled in this study; however, a participant's study doctor may capture results of testing performed for normal clinical care.

Taking part in this research study may involve providing information that a participant considers confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep information safe.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may experience relief of pain and improvement in quality of life. It is possible; the information learned from this study will benefit other people in the future.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

See Section 2.3.1, Known Potential Risks, and Manual of Procedures (MOP) chapter 05, Informed Consent for more details regarding potential risks and benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary outcome of the study is BPI GPS score collected at Weeks 13 and 25. BPI GPS is a self-report measure of pain severity and interference with proven reliability and validity across different pain conditions. It is defined as the average of BPI pain severity and BPI pain interference. BPI pain severity is the average of 4 items asking about current pain and worse, least, and average pain in the past week. BPI pain interference is the average of 7 items that rate how pain interferes with various activities (higher score indicate greater pain interference). We have two	*Brief Pain Inventory-Global Pain Severity.*	*BPI GPS is a self-report measure of pain severity and interference with proven reliability and validity across different pain conditions [1,2]. In this application, BPI GPS is defined as the average of BPI pain severity and BPI pain interference. BPI pain severity is the average of 4 items asking about current pain and worse, least, and average pain in the past week. BPI pain interference is the average of 7 items that rate how pain interferes with various activities (higher score indicate greater pain interference) [59].*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
primary hypotheses (H1 and H2): **H1:** Combination treatment with and without health care professional support is more effective than duloxetine monotherapy in improving GPS. **H2:** Combination treatment <u>with</u> health care professional support is more effective than combination treatment without health care professional support in improving GPS. For further details, see section 9.4.2, Analysis of the Primary Endpoint(s)		
Secondary		
The secondary outcomes will include the two individual components of the BPI GPS: BPI pain severity and BPI pain interference.	*BPI pain severity and* *BPI pain interference*	The BPI assesses pain at its "worst," "least," "average," and "now". The BPI measures how much pain has interfered with seven daily activities, including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep.
Tertiary		
We propose 4 tertiary outcomes to further assess the effect of the interventions on pain.	*Global Rating of Change*	*GRC* assesses overall clinical response. It is consistent with the IMMPACT recommendations for a 7-item patient global change scale [59]. Modified to detect finer gradations of improvement, this scale is sensitive to treatment-related improvements [60].
	PROMIS pain intensity & *PROMIS* pain interference	*PROMIS* Adult Self-Reported Measures on physical health (fatigue, pain intensity, pain interference, physical function, sleep disturbance, pain behavior and sleep-related impairment) and social health (ability to participate in social roles and activities) (*http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis*). *PROMIS* measures were developed and validated with state of the science methods to be psychometrically sound (*http://www.healthmeasures.net/explore-measurement-systems/promis/measure-development-research*).

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	Chronic Pain Coping Inventory (CPCI)	Designed to assess the use of coping strategies that are typically targeted for change in multidisciplinary pain treatment programs, the CPCI can be used as a treatment outcome measure, as a screening measure, and to document the necessity of treatment.
Exploratory		
	Generalized Anxiety Disorder 7-item scale (GAD-7)	*GAD-7* is a validated screening and severity measure for the most common anxiety disorders in primary care (i.e., generalized anxiety, panic, social anxiety, and post-traumatic stress disorder) [61,62]. Higher scores on GAD-7 represent more severe anxiety symptoms. Clinical anxiety is defined as GAD-7 score of ≥10, a cut point validated in previous studies [61,62].
	Patient Health Questionnaire 8-Item Depression Scale (PHQ-8)	*PHQ-8* is a brief self-administered scale that assesses major depressive disorder core symptoms and allows a score (range: 0 to 24) based on the total number and severity of depressive symptoms noted over the previous two-week period. Its validity (including telephone mode of delivery), feasibility and capacity to detect changes of depressive symptoms over time are well established [63-66]. Clinical depression is defined as PHQ-8 score of ≥10, a cut point validated in prior studies [65,67-69].
	The Pain Catastrophizing Scale (PCS)	*PCS* is a 13-item scale that describes the catastrophic thoughts and feelings that people may have in response to pain. The psychometric properties of PCS are well established [70-72] including sensitivity to change [73,74]. The total score ranges 0 (no catastrophizing) to 52 (severe catastrophizing).
	~~*SF-36 physical function* *~~	~~*The Short Form 36 Health Survey Questionnaire (SF-36)* is used to indicate the health status of particular populations, to help with service planning and to measure the impact of clinical and social interventions.~~
	PROMIS Adult measures: physical function, fatigue, social health, sleep disturbance, pain behavior	*PROMIS* Adult Self-Reported Measures on physical health (fatigue, pain intensity, pain interference, physical function, sleep disturbance, pain behavior and sleep-related impairment) and social health (ability to participate in social roles and activities) (*http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis*). *PROMIS* measures were developed and

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		validated with state of the science methods to be psychometrically sound (*http://www.healthmeasures.net/explore-measurement-systems/promis/measure-development-research*).
	Opioid Morphine Equivalent (OME)	*OME* is a measure of daily dose of opioid use. We will use self-reported opioid type[75,76], medical record-based dosage and self-reported daily frequency to calculate the OME, reported in milligrams per day. The OME is calculated by multiplying dosage by daily frequency by a conversion factor for each opioid based on opioid strength[77].
	Health care service utilization	We will extract data on use of different allied health care services from date of enrollment until the one-year anniversary utilizing EMR. The general approach will include models for count data. Length of follow-up will be used as an offset. Poisson models will be used to estimate the mean number of events for each intervention group. Alternatively, negative binomial (NB) models will used if there is evidence of over-dispersion in model diagnostics. The specific health care utilization measures include the following.
	PHQ Anxiety-Depression Scale (PHQ-ADS)	*PHQ-ADS* is a composite of PHQ-8 and GAD-7 scores. PHQ-ADS is a single measure for assessing psychological distress in clinical practice and research [78]. This is especially salient given the frequent co-occurrence of depression and anxiety. PHQ-ADS cut points of 10, 20 and 30 were shown to represent mild, moderate, and severe levels of psychological distress, respectively. We are using cut point of ≥20 to represent moderate level of psychological distress.
	Frequency of Practicing Pain Coping Skills	*Frequency of Practicing Pain Coping Skills*. During the outcome data collection at weeks 13 and 25 we will ask participants how many days they practiced pain coping skills in the past 2 weeks (maximum of 14)[3].
.	*Others.* The study will track medication use but will not control or restrict medication use as part of the study.	To assess co-intervention effect, a treatment survey will inquire about specific treatments the patient has received (opiates and other analgesics, psychotropic medications and use of complementary and integrative health modalities such as acupuncture) for pain since the last follow-up [69].

*We realize that the PROMIS Pain Interference and Pain Intensity are similar to BPI measures. However, the PROMIS measures are required of all NIH HEAL related projects. To reduce participant burden, we will drop SF-36 physical function (given that we already have PROMIS physical function).

4 STUDY DESIGN

4.1 OVERALL DESIGN

PRECICE is a 24-week RCT of patients in the primary care clinics. During the study, participants will be randomized to one of three treatments: (1) [duloxetine + web-based CBT] with health care professional support, vs. (2) [duloxetine + web-based CBT] without health care professional support, vs. (3) duloxetine only. The primary purpose of the phone-based health care professional support is to enhance participant's motivation to engage in the web-based CBT program with regular practice of newly learned pain coping skills during and after the study. See section 9 for the analytical plan including sub-group analyses.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We initially thought of a 3-arm study that compares combination treatment [duloxetine and web-based CBT] vs. duloxetine only vs. web-based CBT only. Such a design would allow us to also compare drug vs. web based CBT. We discarded the idea because it would be unethical to randomize participants with coexisting depression to a treatment arm (i.e., web-based CBT alone) without targeted treatment for depression. In addition, given the general tendency for practicing clinicians to prescribe medication, a more clinically relevant question would be, "What is the additional benefits of web-based CBT when offered concurrently with duloxetine?" Alternatively, a 2-arm RCT (duloxetine only vs. web-based CBT) would be a reasonable design, with combination treatment reserved for those who are non-responders to either duloxetine or CBT alone. However, we rejected this alternative for two reasons: (1) our primary goal is to optimize treatment outcome and a single agent would only yield minimal pain relief; and (2) initiating CBT earlier during treatment may prevent disability and further pain chronicity.

4.3 JUSTIFICATION FOR INTERVENTION

We realized that there are a few disadvantages in using a global endpoint: (1) they generally permit only global, not component-specific, conclusions and are subject to misinterpretation [93]; and (2) treatment effects may be qualitatively different for different components of the composite [93, 94]. Such an endpoint can thus mask a beneficial effect, or lack of effect for one or more of the components of the global endpoint. For this reason, the committee on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has recommended that analyses of each component of the BPI GPS should be reported as well [95]. Thus, in the current application, we have put forth secondary hypotheses to examine the effects of combination treatment (duloxetine + web-based CBT) on the individual component of BPI pain severity and BPI pain interference as secondary endpoints.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment at Week 0, activities associated with the randomized treatment arm, and assessments at Week 1, Week 13, and Week 25. We would consider a participant as having "complete" data if the BPI global pain severity (BPI-GPS) measure is collected at week 25. For further details, see Table 1 in section 1.3 Schedule of Activities. For a description of how we will handle missing data, see Section 9.4.2, "Analysis of the Primary Endpoint(s)".

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

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

1. patients at the primary care clinic with daily pain for 3 months or longer affecting the low back, neck, hip, knee or widespread pain;
2. at least moderate in BPI GPS, defined as a GPS score of 5 or greater[1,2]; and
3. at least age 18 years old or older.

5.2 EXCLUSION CRITERIA

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

1. uncontrolled hypertension - sitting systolic blood pressure >170 mmHg or diastolic blood pressure >100 mmHg at screening - (because duloxetine rarely increases blood pressure);
2. active suicidal ideation;
3. planned elective surgery during the study period (to avoid the confounding effect of possible complicated post-surgery recovery course on the primary outcome);
4. ongoing unresolved disability claims;
5. inflammatory arthritis (e.g., lupus and ankylosing spondylitis);
6. cancer-related musculoskeletal pain;
7. pregnancy;
8. history of bipolar disorder or schizophrenia;
9. narrow angle glaucoma;
10. participant reported chronic kidney disease stage 4, eGFR <30 and/or severe renal impairment (creatinine clearance <30);
11. current use of duloxetine;
12. current use of any of the following medications (to avoid adverse drug-to-drug interactions): tricyclic antidepressant > 25 mg daily dose, monoamine oxidase inhibitors, fluoxetine, sertraline, paroxetine, citalopram, escitalopram, venlafaxine, milnacipran, mirtazapine, , or aripiprazole, serotonin precursors (e.g., tryptophan), and strong CYP1A2 inhibitors (e.g., ciprofloxacin, other fluoroquinolones, fluvoxamine and verapamil);
13. poly-pharmacy (defined as concurrent daily use of 4 or more centrally acting medications for anxiety (anxiolytics), insomnia (hypnotics), anti-psychotic and anticonvulsants (gabapentin and pregabalin are permitted, if subject on a stable dose for at least 4 weeks).

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. This includes those who fall out during the run in phase prior to randomization. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Setting and Recruitment

We will recruit participants from the 271 primary care clinics within the Wake Forest (WF) Baptist Health System, as well as surrounding providers outside of Atrium Health *in North Carolina* .

Subjects Selection Criteria

See sections 5.1 Inclusion Criteria and 5.2 Exclusions Criteria for details.

See MOP chapter 02 for more Recruitment and Retention information.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Web-based Cognitive Behavioral Therapy (web-based CBT). The web-based CBT program is an automated program (i.e., users learn skills with interactive, personalized training without any therapist contact) that includes 8, 35- to 45-minute training sessions, each of which provides an educational rationale and training in cognitive or behavioral pain coping skill drawn from face-to-face CBT [3]. The sessions and features are controlled by a programming component that applies an “expert systems” approach. That is, it pairs decision rules (in the form of computerized tailoring algorithms) with a knowledge database to simulate the behavior and judgment of an expert – in this case, a highly trained therapist experienced in delivering face-to-face CBT. The decision rules customize (tailor) participants’ experience in the program based on their responses and progress through the program. In other words, our web-based CBT retains the therapeutic components and processes (e.g., knowledge, collaborative skills training, self-monitoring, reinforcement, motivational enhancement, and working alliance) underlying the benefits of the face-to-face interventions on which they are based [79].

Participants will complete one session per week (on average) over 12 weeks; this timing offers flexibility in completing sessions (e.g., allowing for personal or medical events to delay completion of some

sessions, which we have found users prefer). Session 1 starts with an overview of the CBT program, and the intervention's therapeutic rationale. This overview is followed by training in the first pain coping skill: progressive muscle relaxation. Sessions 2-7 teach, respectively, brief relaxation skills (i.e., "mini-practices"), activity-rest cycling, pleasant activity scheduling, cognitive restructuring ("coping thoughts"), pleasant imagery, and problem solving. Session 8 reviews each skill to consolidate learning and teaches strategies for long-term skill use. Between sessions, participants are asked to practice their newly learned skill and any skills they learned in past sessions. The program also includes a feature to enhance engagement and facilitate practice. This feature is a section of the program that participants access to self-monitor their progress by reviewing and changing practice goals, recording practices and "coping confidence" (self-efficacy for managing pain), viewing graphic summaries of progress over time, and managing automated practice reminders.

Health care professional-delivered MI. The primary purpose of health care professional contact is to enhance participant's motivation to engage in web-based CBT by encouraging participant's continued use and practice of pain coping skills. Subjects randomized to the [duloxetine + web-based CBT] with health care professional support will receive 6 phone calls from MI trained health care professional at week 3, 6, 10, 14, 18 and 22. Telephone sessions may run for 20 minutes on the average. Similar to our previously tested MI protocol to encourage exercise, the MI intervention has 3 phases:

1. First phase: The first two calls will focus on strategies that enhance motivation to practice newly learned pain coping skills. It involves eliciting from the patient statements (i.e. self-motivational statements) that support the following: a) The patient's recognition of the full nature and extent of the problem, b) The patient's concern about how he or she is currently managing the problem, c) The patient's intention of changing in the direction of adaptive pain management, and d) The patient's optimism that changes are possible.
2. Second phase: This phase is devoted to strategies that strengthen commitment to practice newly learned pain coping skills regularly and consistently. Specifically, the third call would include helping the patient develop a plan for change (i.e. shift from why the patient should consider change to how the patient will make changes) communicating free choice, and reviewing consequences of adaptive vs. maladaptive pain-related behaviors. The fourth phone call would involve asking for a commitment to practice new skills and a plan worksheet.
3. Third phase: The last 2 calls are for follow-through strategies to prevent relapse. To review the changes that have occurred since the last session, the MI-trained health care professional will praise and reinforce any and all approximations of progress. He or she will also review behavioral indicators of motivation, patient's responses to questions concerning reasons for making or maintaining changes, and barriers to adherence. He or she will again obtain a commitment to follow through on the new plan.

Duloxetine. We chose duloxetine as the first line drug because: (1) it has established efficacy for CMP and FDA approval for that indication; and (2) it is available in generic form, which makes it more readily available.

At study entry, all participants will receive duloxetine 30 mg once daily for one week. At Week 1, subjects who tolerate the 30 mg daily dose and do not have chronic kidney disease stage 3 will begin 60 mg once daily for 24 weeks. Subjects with CKD-3 tolerating 30mg daily, will continue on 30mg for 24 weeks. At week 25, participants will return to the research clinic for outcome assessments.

To assure safety of study participants, subjects will complete a symptom monitoring form (formerly labeled as medication side effects checklist) at week 1, week2, week 4, week 13 and week 25. The subject may be contacted via text messaging as an adjunct to phone calls to assess duloxetine symptoms

monitoring at weeks 2 and 4 and for appointment reminders. The medical safety officer will be informed of any AEs (at week 1, week 2, week 4, week 13 and week 25) that require medical attention. For AEs that require medical attention, the study Medical Safety Officer will directly contact the participant to provide immediate care and guidance.

At the last study visit (week 25), participants who would like to stop the medication will be provided duloxetine 30 mg once daily for 7 days and medication treatment will then stop (tapering regimen). Subjects already taking 30 mg daily will stop dosing at their week 25 visit. Those who would like to continue duloxetine will be prescribed a 2-week supply of duloxetine and will be instructed to talk to their primary care provider (PCP). In addition, the investigator will send a Wake One message to the PCP to consider continuation of duloxetine.

Other treatments. The use of over-the-counter analgesic medications will be permitted and assessed to adjust for co-intervention differences between groups in the analyses.

6.1.2 ADMINISTRATION AND/OR DOSING

See Duloxetine dosing information under Section 6.1.1.

See MOP chapter 09, Intervention, for more details.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Health care professional-delivered MI.
To assess treatment fidelity, 10% of all audiotaped MI sessions will be reviewed. A qualified MI consultant , will use the MITI 4 method in evaluating treatment integrity[80]. The MITI method represents a focused tool for evaluating competence in the use of MI.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The PI and the analysis team at the clinical site will remain blinded to group assignment throughout the study. Randomization will be stratified by number of pain sites (≤2 vs. ≥3 sites) and opioid use. Number of pain sites is included as a stratification variable, since it has been associated with worse outcomes [81-83].

The data team , who is blinded of treatment group assignment, has the primary responsibility of analyzing outcome data throughout the study.

Randomization will be accomplished through the REDCap Randomization Module. REDCap helps implement a defined randomization model within the study project, by allowing users to 1) Define all of the randomization parameters; 2) Create and upload a custom randomization table (i.e., allocation list). The table serves as a lookup table for deciding how to randomize subjects/records. The module also monitors the overall allocation progress and assignment of randomized subjects.

For more randomization details, see MOP chapter 07, Randomization.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Importance of Maintaining and Enhancing Treatment Outcome of Web-based CBT

As in the in-person CBT protocol, participants in a web-based CBT program are typically asked to practice each new cognitive or behavioral pain coping skills after learning it. Fundamental to the long term effectiveness of CBT is the requirement that pain coping skills are applied or practiced on a regular basis. In a study of traditional CBT for chronic pain, pre- to post-treatment changes in pain control and catastrophizing mediated the effects of CBT on pain and activity interference[52]. In fibromyalgia, treatment outcomes were most closely related to 5 coping strategies or skills: decreased guarding, increased use of exercise, seeking support from others, activity pacing, and use of coping self-statements [30]. Unfortunately, as with face-to-face CBT programs, maintenance of clinical improvements from web-based CBT has **not** been consistently observed [50] partly due to reduced use of cognitive and behavioral pain coping skills over time.
Rini C, Keefe F et al. evaluated the effectiveness of web-based CBT (**+** physiotherapist-guided home exercise delivered through Skype) to 148 persons with chronic knee pain. Improvements in pain and function with the intervention were large at 3 months (immediate post-intervention) and were greater than those in the control group[3]. Benefits were apparent at follow-up, although between group differences were reduced. Further, 64% of the CBT practice exercises (i.e., relaxation, coping thoughts, pleasant imagery, distraction, problem solving, activity-rest cycling, pleasant activity scheduling) were completed at 3 months with numbers decreasing during follow-up to 41%. Based on these findings, treatment strategies are needed to motivate continuous use or practice of pain coping skills to achieve long term success.

MI to Enhance Benefits of Web-based CBT

MI is an effective counseling approach to elicit behavior change (e.g., from sedentary lifestyle to physically active lifestyle, from poor food choices to healthier food choices to achieve weight loss, etc.) [53-57]. In contrast to delivering simple advice, a MI-trained health care professional helps a patient discuss the pros and cons, and the barriers and solutions to behavior change; consequently, enhancing self-efficacy. Self-efficacy determines whether an individual attempts a given task, the degree of persistence when difficulty is encountered and ultimate success or failure of the behavior.

Preliminary Data: In our RCT study [58], 216 participants with fibromyalgia were randomized to MI to increase physical activity vs. education (attention) control. Over a 12-week period, participants received either **six** telephone-delivered MI or educational (attention control) instructions. Post intervention, MI was superior to control in increasing the number of weekly hours of self-report physical activity. At follow up, more MI participants than controls exhibited meaningful improvement in global severity. Additionally, participants in the MI group had a significantly greater improvement (i.e., walked longer distance) in the 6-minute walk test compared to controls.

Given our success on the use of telephone-delivered MI, it is reasonable to hypothesize that six sessions of telephone-delivered MI to increase participant's continued practice of pain coping skills will enhance treatment outcomes.

The web-based CBT program (painTRAINER) utilizes online tools as well as a workbook to help participants track goals for completing pain coping modules and practicing coping skills, log practices, log coping confidence, and view progress.

See Table 1 in Section 1.3, Schedule of Activities, for a list of study measures and time points for data collection.

6.5 CONCOMITANT THERAPY

For this protocol, participants may use the medications that they were on at study entry including opioid and non-opioid analgesics for pain control, including over-the-counter medications and dietary supplements, and prescribed medications. Medication usage will be assessed at each IPV and documented in the relevant Case Report Form (CRF).

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a subject discontinues from the study intervention but not from the study, remaining study procedures will be completed as indicated by the study protocol. 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:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

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 a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Participant Status form. 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, will not 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 one IPV and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The staff will attempt to contact the participant, reschedule the missed visit, 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.

- Study staff will utilize a participant provided alternate contact list, if necessary, to reach the participant.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.

- We will use multiple methods to contact participants who drop out, including text messaging and/or email.

- 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 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

The specific timing of procedures/evaluations to be done at each study visit are captured in Section 1.3, Schedule of Activities (SoA) including physical examination-based assessments, administration of

questionnaires and interviews, and collection of health care utilization data from the participant's EMR. Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements will be followed, as applicable.

Also, see Section 3 for a full list of Objectives and Endpoints.

8.2 SAFETY ASSESSMENTS

1. A Safety Monitoring Committee (SMC) will be formed to assure human subject safety and study integrity.
2. The PI and the study team will meet monthly to review all serious, unexpected and on-site AEs and make recommendations for any changes in reporting, consent or study activities.
3. A site visit program will 1) include an experienced data auditor who will review data to ensure that study procedures are understood and carried out correctly and 2) provide a mechanism to encourage the effective and standardized delivery of recruitment efforts, intervention programs, and the collection of appropriate and valid data. See MOP Chapter 14, Quality Control (QC), for additional information
4. We will minimize duloxetine-related risks by doing the following:
    a. Study staff will administer a study medication Symptom Monitoring Form at five different occasions (weeks 1, 2, 4, 13 and 25) and will report every adverse effect (AE) to the medical safety officer (an internal medicine physician with active primary care clinic practice). For AEs that require medical attention, the medical safety officer will directly contact the participant to assess the need for adjustment or discontinuation of the study medication.
    b. Participants will be assessed for suicidal ideation. The medical safety officer will be notified of low and moderate risk individuals and will direct study personnel how to proceed. Emergency procedures will be employed if a participant is considered high risk.
    c. Urine pregnancy test will be performed at baseline (week 0) and at week 13 for all females of childbearing potential. We will ask pregnancy status at each study visit. We will ask subjects who become pregnant while in the study to discontinue duloxetine. These subjects will not be withdrawn from the study. Importantly, in the informed consent, we will include the rare side effects of Serotonin–norepinephrine reuptake inhibitor (e.g., duloxetine) exposure late in the third trimester.
    d. The medical safety officer or the investigator will review AEs and determine likelihood that AEs are related to study drug.
5. Our trained study staff will ask about emotional distress related to the web-based CBT and report any concerning issues to the medical safety officer.
6. Data monitoring plan
    a. Web-based scripted data entry forms will be utilized to guide staff through the administration of screening instruments administered via phone.
    b. Once a subject passes screening and is formally enrolled in the study, study staff will use a custom data collection and randomization engine to collect demographic information, receive the randomization by stratum, and validate that inclusion and exclusion criteria have been appropriately tested.
    c. Only the following people or organizations will be granted access to study records and data: study investigators, research team, Institutional Review Boards, the FDA, and the NIH (NINR).
    d. Electronic case report forms (eCRFs) will be used for all data collection procedures. The data security measures will encompass the following functions:

i) *Data Tracking* – will be used to provide the status of enrollment, number of complete data collection forms and number of forms.
ii) *Data Entry* – systems will be in place to allow easy-to-use interfaces to minimize errors.
iii) *Data Editing* – The need for data editing will be minimal because systems will be in place to prevent erroneous data entry.
iv) *Reporting* – The study website will generate reports on a weekly basis of the number of patients enrolled, the number of missing data fields and the number of missing phone-delivered intervention sessions for the combination group (duloxetine + web-based CBT) with health care professional support. Periodic and ad-hoc reporting will be utilized to show subject recruitment and retention data.
v) *Statistical Analysis* – The data management team will perform data analysis with SAS.

f. Quality assurance (data integrity and validity) measures will be as follows:
i) Real-time data validation will be utilized to ensure data quality at the time of entry.
ii) Data and form checks will be completed by the WFDM team.
iii) Missing data will be monitored on a regular basis and the project manager on the study team side will be informed of missing data daily via "red flag" reminders in the database.
iv) The PI will discuss the rate and type of missing data during the bi-monthly teleconferences.
v) Data entry safeguards will prevent the erroneous entry of data that would fall outside the bounds of data that would be acceptable for a particular field.
vi) Dr. Ang will review weekly updates generated by the data management team to monitor missing data rates, and response times to red flag reminders.

g. Data confidentiality will be ensured in the following ways:
i) Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented**.**
ii) Alert values for medically relevant procedures (e.g., blood pressure, pulse rate, and suicidal ideation) will be developed, and a system will be in place to alert the medical study officer, depending on the urgency of the values.
iii) Confidentiality of data will be maintained by using research identification numbers that uniquely identify each individual.
iv) Safeguards will be established to ensure the security and privacy of participants' study records.
v) Appropriate measures will be taken to prevent unauthorized use of study information. Data other than demographic information will not use names as an identifier.
vi) Research records will be kept in a locked room at the research office.
vii) The files matching participants' names and demographic information with research ID numbers will be kept in a locked computer file (password protected) that uses a different key from that of all other files. Only trained and certified study personnel will have access to these files, and they will be asked to sign a document that they agree to maintain the confidentiality of the information.
viii) After the study is completed, local data will be stored with other completed research studies in a secured storage vault.
ix) In compliance with HIPAA and the Standards for Privacy of Individually Identifiable Health Information of the Department of Health and Human Services, we access personal health information and medical records only after receiving signed informed consent.

See MOP chapter 12, Safety Monitoring and Serious Adverse Events, for more details of the monitoring entity, monitoring procedures, and data monitoring plan.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

An **adverse event** is any undesirable experience that occurs during the study, whether or not it is associated with the interventions in a participant.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An AE is **serious** if it results in death, is life-threatening, requires inpatient hospitalization or prolongs an existing hospitalization, results in a persistent or significant disability/incapacity, or might require medical or surgical intervention to prevent one of the outcomes, such as treatment in the emergency room for severe injurious falls.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

As part of the safety monitoring system**,** AEs reported to study staff at any time will be reviewed by the medical safety officer, who will identify, assess severity and relatedness to study drug, and if needed, manage the event. The study staff will report AEs and/or any unanticipated problems, to the medical safety officer. For AEs that require medical attention, the medical safety officer will directly contact the subject.

Safety related events will be reported within 10 days, as required by the SMC and the IRB that are responsible for study oversight.

For ongoing participant safety, events are assessed by the medical safety officer or Investigator to determine if they are Serious, Unexpected, or Related to study participation. If the event is reportable to the IRB, an event evaluation form will be completed that will include a description of the event, a classification of seriousness, assessment of potential relationship to the intervention, assessment of need for change in the consent or the study activities, a summary of known prior health issues, event outcome and a classification of the main organ system involved. The classification of potential relationship to the intervention is as follows.

Definite - Temporal pattern + Known or expected AE response pattern + Confirmed by stopping the intervention + Reappearance of AE on re-challenge

Probable - Temporal pattern + Known or expected AE response pattern + Confirmed by stopping the intervention + could not be explained by participant's clinical state

Possible - Temporal pattern + Known or expected AE response pattern + could have been produced by a number of other factors

Unknown - Relationship for which no evaluation can be made.

Not related - AE for which sufficient information exists to indicate that the cause is unrelated to the study intervention

The medical safety officer or the Investigator will determine the attribution/relatedness of each AE. The PI will report AEs to NINR every 6 months, including actions taken by the IRB as a result of such AEs.

See MOP chapter 12, Safety Monitoring and Serious Adverse Events, for more details of adverse and serious adverse events (SAEs) including the Study Medication Symptom Monitoring Form, the Adverse Event Form, and the Suicide Algorithm.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

See section 8.3.3.1 above for classification of potential relationship to the intervention.

8.3.3.3 EXPECTEDNESS

The medical monitor or Investigator will be responsible for determining whether an 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 procedures.

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

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care.

All AEs, not otherwise precluded per the protocol, will be captured on the AE Form (included in MOP chapter 12, Safety Monitoring and Serious Adverse Events). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures, and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution or stabilization.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if 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. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Clinic staff and the study safety officer will record events with start dates occurring any time after informed consent is obtained. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

See section 8.3.3.1 above and MOP chapter 12, Safety Monitoring and Serious Adverse Events, for additional information on AE reporting.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, study team members will be responsible for reporting AEs, SAEs and unanticipated events that meet IRB reporting criteria, as soon as possible, but no later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

See section 8.2 Safety Assessments for pregnancy related policy.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

An unanticipated problem is any event, incident, experience, or outcome (including, but not limited to, adverse events and serious adverse events) which occurs in a research study and **meets ALL** of the following criteria:

- Unexpected in nature, frequency, or severity (not articulated in the study protocol, informed consent or Investigator's Brochure or not expected as a consequence of the natural history of a disease under study)

- Related or possibly related to participation in the research (there is a reasonable possibility the that the event, incident, experience, or outcome may have been caused by the drug/device, procedures or interventions involved in the research)

- Places subjects or others at a greater risk of harm than was previously known or recognized (causes physical, psychological, economic, or social harm to a human subject; increases the risk of harm of any kind; or otherwise compromises subject's safety, rights, welfare, or privacy).

Reportable events are not limited to physical injury, but also include psychological, economic, and social harm. Reportable events may arise as a result of the use of drugs, biological agents, devices, procedures or other interventions, or as a result of the use of questionnaires, surveys, observations or other interactions with research subjects. All breaches of confidentiality are reportable events. Reporting to the IRB is required regardless of the funding source or study sponsor.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB and to the Data Coordinating Center (DCC). 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:

- UPs that are SAEs will be reported to the IRB, the DCC, and the NINR Program Officer within 48 hours of the investigator becoming aware of the event
- Any other UP will be reported to the IRB, the DCC, and the NINR Program Officer within 7 calendar days of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) and the supporting agency head (or designee)
- OHRP reporting is made by the IRB in accordance with federal and institutional requirements

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Any unanticipated problem resulting in a change to the protocol that might affect participant's participation in the study will be reported to the participant should the IRB require this and the IRB will make the decision if re-consenting is needed.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

We have two primary hypotheses (H1 and H2):

H1: Combination treatment with and without health care professional support is more effective than duloxetine monotherapy in improving BPI GPS.

The primary comparison will be the combination treated groups (with and without health care professional support) vs. duloxetine group.

H2: Combination treatment with health care professional support is more effective than combination treatment without health care professional support in improving BPI GPS.

The primary comparison will be combination group with health care professional support vs. without health care professional group.

Exploratory hypothesis: Compared to those without comorbid psychological distress, participants with comorbid psychological distress are more likely to respond to combination therapy (with and without health care professional support) than to duloxetine monotherapy.

9.2 SAMPLE SIZE DETERMINATION

With 280 participants and 20% loss to follow-up, we will have 75 evaluable participants in each treatment group. Based on published literature (*Kroenke K et. al JAMA July 2014*), the estimated standard deviation (SD) for BPI GPS score is 2.2. Assuming a moderate correlation of 0.5 between baseline and follow-up measures, we estimate that the SD in an analysis of covariance (ANCOVA) will be approximately 1.9. Therefore, we will have 90% power to detect a difference of -1 in BPI GPS score between combination groups (n= 150) and drug only group (n=75) for Aim 1. The power will be 83% power for comparison between combination with health care professional (n=75) and combination without health care professional (n=75) for Aim 2. All power calculations are based on two-sided t tests with alpha level of 0.025 to adjust for Bonferroni correction of testing two main hypotheses.

9.3 POPULATIONS FOR ANALYSES

WF Baptist Health. We have identified 9,243 unique individuals in the age range of at least 18 years old or older; seen at the primary care clinic over the past 12 months; and who received one of the relevant ICD 10 codes. The pool of potentially eligible participants (N=9,243) is large enough to get us to our target sample size of 250 at WF Baptist Health. This pool of 9,243 individuals has the following characteristics: Gender: 62% females and 38% males; Race: 21% African Americans, 2.8% Hispanics, 1% Asians and 72.2% Whites. Over the past 4 months we surveyed 86 patients with CMP (48% females; mean age= 51 years old) who were seen in one of WF Baptist Health primary care centers. We found that 58 (67%) patients continue to have a significant amount of pain despite current treatments, and also reported that pain prevented them from working or doing the things they enjoy almost every day. From these 58 patients, 50 (86%) have expressed willingness to participate in clinical studies to help reduce their pain and improve their quality of life.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

See the following sections for details.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Primary Outcome

The primary outcome of the study is BPI GPS score collected at Weeks 13 and 25. BPI GPS is a self-report measure of pain severity and interference with proven reliability and validity across different pain conditions. The overall score is defined as the average of 11 items. Two subscales are also defined: BPI pain severity and BPI pain interference. BPI pain severity is the average of 4 items asking about current pain and worse, least, and average pain in the past week. BPI pain interference is the average of 7 items that rate how pain interferes with various activities (higher score indicate greater pain interference). All study participants will be analyzed according to randomized treatment assignment regardless of adherence to the treatment protocols. We have two primary hypotheses (H1 and H2):

H1: Combination treatment with and without health care professional support is more effective than duloxetine monotherapy in improving BPI GPS.
H2: Combination treatment with health care professional support is more effective than combination treatment without health care professional support in improving BPI GPS.

Research has shown that the use of ANCOVA with baseline measure as a covariate is an optimal method in both design and analysis of trials with a continuous primary outcome. Compared to the use of change score as the primary outcome, ANCOVA is generally superior in terms of efficiency, precision, and power. Therefore, the primary analysis will be Week 13 and 25 BPI scores as a primary outcome while adjusting for baseline measurement.

In primary analysis, we will fit a LMM to account for the correlation among the repeated measures. The model will include indicator variables for intervention arms, visit, and the interaction term. Covariates will include the pre-randomized measure of BPI global score, the stratification factor opioid use, and the number of pain sites. Average follow-up BPI global pain scores for the 3 intervention groups will be estimated using least square means. Two different contrasts will be constructed to test H1 and H2 separately, each at the significance level of 0.025.

We will conduct several sensitivity analyses to evaluate the robustness of the results. First, we will use inverse probability weighting (IPW) to account for missing data. We will identify the baseline characteristics that may be associated with lost to follow-up and derive weights for use in IPW analysis. Additional sensitivity analysis will include indicators of new pain related medication taken, and any use of complementary treatment.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary Outcomes
The secondary outcomes will include the two individual components of the BPI GPS: BPI pain severity and BPI pain interference. We will use similar LMMs described for the primary outcome analysis.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

N/A

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Subgroup Analyses

We will conduct subgroup analysis using LMMs to test the interactions between intervention arm (with and without health care professional support vs. monotherapy) and baseline characteristics. The subgroups include comorbid psychological distress, use of opioid, and number of painful body sites (dichotomized at the median value). The interaction will be tested at the 0.10 level of significance. A significant interaction is indicative of potential moderating effect of baseline characteristic such as psychological distress for predicting the mean BPI GPS score under combination therapy.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

Tertiary outcomes

We propose the following 4 tertiary outcomes to further assess the effect of the interventions on pain. We will use similar LMMs described for the primary outcome analysis.

1. *GRC*

   GRC assesses overall clinical response. It is consistent with the IMMPACT recommendations for a 7-item patient global change scale [59]. Modified to detect finer gradations of improvement, this scale is sensitive to treatment-related improvements
2. PROMIS pain intensity
3. PROMIS pain interference

   PROMIS (*http://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis*) Adult Self-Reported Measures on physical health (fatigue, pain intensity, pain interference, physical function, sleep disturbance, pain behavior and sleep-related impairment) and social health (ability to participate in social roles and activities). PROMIS measures were developed and validated with state of the science methods to be psychometrically sound (*http://www.healthmeasures.net/explore-measurement-systems/promis/measure-development-research*).
4. CPCI

Exploratory outcomes

1. *GAD-7*

   GAD-7 is a validated screening and severity measure for the most common anxiety disorders in primary care (i.e., generalized anxiety, panic, social anxiety, and post-traumatic stress disorder) [61,62]. Higher scores on GAD-7 represent more severe anxiety symptoms. Clinical anxiety is defined as GAD-7 score of ≥10, a cut point validated in previous studies [61,62].
2. PHQ-8

   PHQ-8 is a brief self-administered scale that assesses major depressive disorder core symptoms and allows a score (range: 0 to 24) based on the total number and severity of depressive symptoms noted over the previous two-week period. Its validity (including telephone mode of delivery), feasibility and capacity to detect changes of depressive symptoms over time are well established [63-66]. Clinical depression is defined as PHQ-8 score of ≥10, a cut point validated in prior studies
3. PCS

PCS is a 13-item scale that describes the catastrophic thoughts and feelings that people may have in response to pain. The psychometric properties of PCS are well established [70-72] including sensitivity to change [73,74]. The total score ranges 0 (no catastrophizing) to 52 (severe catastrophizing).

~~4. SF-36 physical function~~

~~This 10-item scale inquires about the subject's perception of their limitations in the performance of various types of physical activities. Scale scores can range from 0 to 100, with higher scores indicating better functioning.~~

4. PROMIS Adult measures: The weight of evidence supports the appropriateness of using PROMIS measures across different medical conditions including various CMP conditions [85].

   Physical function
   Fatigue
   Social health
   Sleep disturbance
   Pain behavior

5. *OME*

   OME is a measure of daily dose of opioid use. We will use self-reported opioid type[75,76], medical record-based dosage and self-reported daily frequency to calculate the OME, reported in milligrams per day. The OME is calculated by multiplying dosage by daily frequency by a conversion factor for each opioid based on opioid strength[77].

6. Health care service utilization

   We will extract data on use of different allied health care services from date of enrollment until the one-year anniversary utilizing EMR. The general approach will include models for count data. Length of follow-up will be used as an offset. Poisson models will be used to estimate the mean number of events for each intervention group. Alternatively, negative binomial (NB) models will used if there is evidence of over-dispersion in model diagnostics. The specific health care utilization measures include the following.

   7.1 Number of <u>new</u> referrals to other specialties or allied health services from <u>enrollment date to the one-year anniversary</u>

   a. Orthopedic surgery
   b. Spine center
   c. Neurosurgery
   d. Pain specialty
   e. Physical Medicine/Rehabilitation (PMR)
   f. Rheumatology
   g. Integrative Medicine
   h. Psychiatry
      i. Medication
      ii. Counseling
      iii. Medication + counseling
   i. Quartet system for PCP – psychiatry/psychology referral (not currently link with Wake One)
   j. Physical therapy
   k. Occupational therapy

   7.2 Number of <u>visits</u> to each specialty or allied health services from <u>enrollment date to the one-year anniversary</u>

   l. Orthopedic surgery
   m. Spine center

n. Neurosurgery
o. Pain specialty
p. Physical Medicine/Rehabilitation (PMR)
q. Rheumatology
r. Integrative Medicine
s. Psychiatry
    i. Medication
    ii. Counseling
    iii. Medication + counseling
t. Quartet system for PCP – psychiatry/psychology referral (not currently link with Wake One)
u. Physical therapy
v. Occupational therapy

7.3 Number of orthopedic or musculoskeletal surgeries from enrollment date to the one-year anniversary. See attached relevant CPT codes.

8 *PHQ-ADS* is a composite of PHQ-8 and GAD-7 scores. PHQ-ADS is a single measure for assessing psychological distress in clinical practice and research [78]. This is especially salient given the frequent co-occurrence of depression and anxiety. PHQ-ADS cut points of 10, 20 and 30 were shown to represent mild, moderate, and severe levels of psychological distress, respectively. We are using cut point of ≥20 to represent moderate level of psychological distress.

9 *Frequency of Practicing Pain Coping Skills*. During the outcome data collection at weeks 13 and 25 we will ask participants how many days they practiced pain coping skills in the past 2 weeks (maximum of 14)[3].

10 *Others.* The study will track medication use but will not control or restrict medication use as part of the study. To assess co-intervention effect, a treatment survey will inquire about specific treatments the patient has received (opiates and other analgesics, psychotropic medications and use of complementary and integrative health modalities such as acupuncture) for pain since the last follow-up [69].

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

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 will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. We will make every attempt to send (via regular mail or email) the informed consent to participants before the first study visit to allow participants to carefully review the informed consent document.

See MOP chapter 05, Informed Consent, for consent materials.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

To be eligible for participation in the PRECICE study, participants must have the capacity to give their own informed consent. To avoid pressuring the participant, only one person associated with the study should be present when the participant reviews the consent forms. The setting in which consent is obtained will be as private as possible so participants can freely ask questions without embarrassment.

The participant should be fully informed and be given ample time to consider the pros and cons of participation in the study. The participant should be encouraged to discuss the study with anyone they wish.

The participant should be given a copy of the informed consent forms after they are signed and dated by the participant and study team member obtaining informed consent. Even though participants are free to withdraw from the study at any time, the consent form spells out our obligations to the participant and the participant's obligations to the study while he or she is a subject.

Participants should be encouraged to keep the consent forms. The consent forms contain useful information about the study which participants may want to review from time to time. After the participant has signed the consent form, forward the consent form to the PI for his signature.

Anyone who signs a consent form should personally date it. If consent is obtained the same day that the participant's involvement in the study begins, the participant's study record should document that consent was obtained prior to participation in the research. A general statement for source documentation should be included, such as, "All the required elements of informed consent were presented to the patient. Voluntary consent was obtained, and the patient's questions were answered prior to initiation of any research procedures."

For further details, see MOP chapter 05, Informed Consent.

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, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, FDA, or other relevant regulatory or oversight bodies (OHRP, SMC).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the IRB, regulatory agencies or representatives from companies or organizations supplying the product, 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.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the WFHS 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. The study data entry and study management systems used by the clinical site and by WFHS 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 WFHS DCC.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

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

When the study is completed, access to study data will be provided through the NIH Data Repository.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Dennis Ang, MD, MS Principal Investigator Chief of Rheumatology and Immunology	William Y. Rice, III Co-Investigator, Associate Professor, General Internal Medicine
Wake Forest Baptist Medical Center	Wake Forest Baptist Medical Center
Medical Center Blvd. Winston-Salem, NC 27157	Medical Center Blvd. Winston-Salem, NC 27157
336.716.4209 (work)	336.716.3787 (work)
dang@wakehealth.edu	wrice@wakehealth.edu

Study leadership includes a Statistical/Data Management team, a Wake Forest Baptist Research team, and Study Intervention teams for Psycho-education and Study Medication. *See MOP chapter 16, Publications and Other Study Policies, for a list of study team roles and responsibilities of those involved in the conduct, management, or oversight of the trial.*

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a SMC composed of individuals with the appropriate expertise, including two clinical investigators (one with expertise in clinical trials and the second with expertise in behavioral-based intervention) and one PHD level biostatistician. Members of the SMC will be independent from the study conduct and free of conflict of interest.

The SMC will meet twice a year and will be provided with a report that will contain safety data summaries, patient demographics and compliance data, recruitment, visit schedules, missed visits, outcomes and Medical Event Forms and any other AEs. Each member of the SMC will be given a detailed progress report at least two weeks before the meeting. The SMC will be able to request specific information and analyses from the PI's research team for monitoring purposes at any time during the study. Finally, the SMC will make recommendations to the PI regarding continuation, termination, or other modifications to the study based on observed AEs of the treatment under study. The PI will inform the NINR (National Institute of Nursing Research) project officer of any recommendations from the SMC. The NIH program officer will attend the SMC meeting on as needed basis.

10.1.7 CLINICAL MONITORING

Data monitoring will be 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/amendment(s), with ICH GCP, and with applicable regulatory requirement(s). Monitoring activities will be as follows:

- The data team will oversee the data integrity of the current study.
    - Participant forms will be reviewed throughout the study. Initially, all forms from the first ten randomized participants will be reviewed. This will include all forms entered in the data entry system, the consent forms, and the informed consent tracking form. This set of ten forms will be sent to for review as they are completed.
    - Ten percent of informed consent forms will be reviewed on a periodic basis, to verify that the forms are legible and that they have been filled out correctly and completely.
- Study staff will be trained to administer and review all questionnaires and data collection forms before the participant leaves the clinical research unit. Additionally, the study staff will perform monthly QC checks in the data entry system.
- Site study team meetings may also be conducted, if consistent departures from the Protocol and MOP are detected. Retraining may be done as needed during these visits, depending on the availability of staff.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Study-wide QC is the ultimate responsibility of the PRECICE clinical center and the DCC. The PRECICE Project Coordinator at the clinical research site must become familiar with PRECICE requirements and schedule clinic activities so that there is adequate time for clinic staff to carry out their responsibilities while meeting quality standards.

The clinical research site will perform internal quality management of study conduct, and data collection, documentation, and completion. The clinical research site will follow a common quality management plan.

QC procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Study data will be captured in RedCap(see **Section 10.1.9, Data Handling and Record Keeping**)

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, 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 will be the responsibility of the clinical trial staff at the site under the supervision of the investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a REDCap secure web platform for building and managing online databases and surveys. REDCap is a 21 CFR Part 11-compliant data capture system available through the Wake Forest School of Medicine Clinical and Translational Science Institute. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

As required for NIH grantees, PRECICE study documents will be retained for a period of three years from the date of the Federal Financial Report (FFR) submission.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, ICH GCP, or MOP requirements. The noncompliance may be either on the part of the participant, the investigator,

or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation. All deviations will be addressed in study source documents, reported to the NINR Program Official and WFHS sponsor. Protocol deviations will be sent to the reviewing IRB per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in 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:

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.

The project will comply with all NIH HEAL Initiative Data Sharing policies.
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.

The NIH Genomic Data Sharing Policy, which applies to all NIH funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research is not applicable for this study.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. 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. WFHS 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.

10.2 ADDITIONAL CONSIDERATIONS

In case of **complete** shutdown of all clinical research activities,

1. Participants will complete the questionnaires online.
2. We will mail the medication (and urine pregnancy test if relevant) to the participant's home address. Participant will take a picture of the result of the pregnancy test and email it to the research staff.

In case of **partial** shutdown of all clinical research activities,

1. Participants will complete the questionnaires online.
3. Participants will pick up the medication (and urine pregnancy test if relevant) on a designated pick up area within the medical center. Participant will take a picture of the result of the pregnancy test and email it to the research staff.

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BPI	Brief Pain Inventory
CBT	Cognitive Behavioral Therapy
CFR	Code of Federal Regulations
CMP	Chronic Musculoskeletal Pain
CPCI	Chronic Pain Coping Inventory
CRF	Case Report Form
DCC	Data Coordinating Center
eCRF	Electronic Case Report Forms
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FFR	Federal Financial Report
GAD-7	Generalized Anxiety Disorder 7-item scale
GCP	Good Clinical Practice
GPS	Global Pain Severity
GRC	Global Rating of Change
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IPV	In-person Visit
IRB	Institutional Review Board
LMM	Linear Mixed Effects Model
MI	Motivational Interviewing
MITI 4	Motivational Interviewing Treatment Integrity Code
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health

OHRP	Office for Human Research Protections
OME	Opioid Morphine Equivalent
PCP	Primary Care Provider
PCS	Pain catastrophizing scale
PCST	Pain-coping Skills Training
PHQ-8	Patient Health Questionnaire 8-Item Depression Scale
PHQ-ADS	PHQ Anxiety-Depression Scale
PI	Principal Investigator
PRECICE	Pain Response Evaluation of a Combined Intervention to Cope Effectively
PROMIS®	Patient-Reported Outcomes Measurement Information System
QC	Quality Control
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SF-36	The Short Form 36 Health Survey Questionnaire
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
UP	Unanticipated Problem
US	United States
WFDM	Wake Forest Data Management
WFHS	Wake Forest Health Sciences

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
1	05/13/2020	IRB approved	Original version
2	12/08/2020	Protocol modified to NIH preferred format	NIH provided "NIH Protocol Template for Behavioral and Social Sciences Research Involving Humans"
3	12/17/2020	Protocol modified to include NIH suggested changes.	Response to NIH reviewers' feedback.
4	01/14/2021	At week 25, participants who would like to continue duloxetine will be prescribed a 2-week supply of duloxetine. Modified Table 1 to indicate Pre-Screening.	The 2-week supply will give participants enough time to ask their PCP for a refill. Modified Table 1 to indicate Pre-Screening.
5	03/11/2021	Change to the calculation of our primary outcome on Page 30.	Compared to the use of change score as the primary outcome, ANCOVA is generally superior in terms of efficiency, precision, and power. Therefore, the primary analysis will be Week 13 and 25 BPI scores as a primary outcome while adjusting for baseline measurement.
	04/14/2021	Changed "nurse" to "coach" throughout the protocol.	It was determined by speaking with the hiring department and nursing management that the coaching did not have to be done by a nurse. The Informed Consent document indicates "coach".
	04/19/2021	Updated Table 1, footnote.	Made correction to footnote "e": "At week 1, participants will receive duloxetine 60 mg once daily for 24 weeks".
6	07/19/2021	Added footnote "i" to Table 1. Added text to Section 6.1.1. Added using text messaging as an adjunct to our phone calls to assess duloxetine symptoms monitoring at weeks 2 and 4 and for appointment reminders.	We have observed that a substantial proportion of participants perceive the phone calls as "burdensome". This is manifested by not answering or not returning our calls. To address this issue, we have

			added the option of using text messaging as an adjunct to our phone calls.
7	03/28/2022	Changed “coach” to “health care professional” throughout the protocol and updated the analysis plan text regarding painful body sites stratification.	Changed “coach” to reflect a more generic term. The health care professionals trained in MI may range from a coach to PhD level. Updated the analysis plan based on decisions we made about the painful body sites stratification.
8	11/01/2022	Updated description of site enrollment facilities to add providers outside of the Atrium Health system	Enhance recruitment
		5.2 Eligibility criteria: revised to add inclusion of CKD-3 patients	Enhance recruitment
		5.2 Eligibility criteria: clarified criteria for uncontrolled hypertension	Safety
		5.2 Eligibility criteria: clarified use of gabapentin and pregabalin	Safety
		6.1.1 Revised to include drug dosing for subjects with CKD -3; text messaging may be used to contact subjects; clarified end of study drug discontinuation procedure	Safety
		10.1.7 Revised to reflect data collection oversight process	Clarification
		Editorial revisions and administrative changes throughout	Clarification

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