Study Title: The Back Pain Consortium Research Program (The BACPAC Study)

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University of Michigan Mechanistic Research Center –

The Back Pain Consortium Research Program

(The BACPAC Study)

Study Protocol

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Principal Investigators:
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MICHIGAN MEDICINE
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BACPAC

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Statement of Compliance

This trial will be carried out in accordance with the 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) and research best practices. The PIs and all study team members who are responsible for the conduct, management, or oversight of NIH-funded clinical trials will complete Human Subjects Protection and best practices training.

The protocol, informed consent document, and all participant materials will be submitted to IRBMED for review and approval. Approval of both the protocol and the consent documents will be obtained before any participant is consented. Any amendment to the protocol will be submitted for review and approval by IRBMED 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 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:

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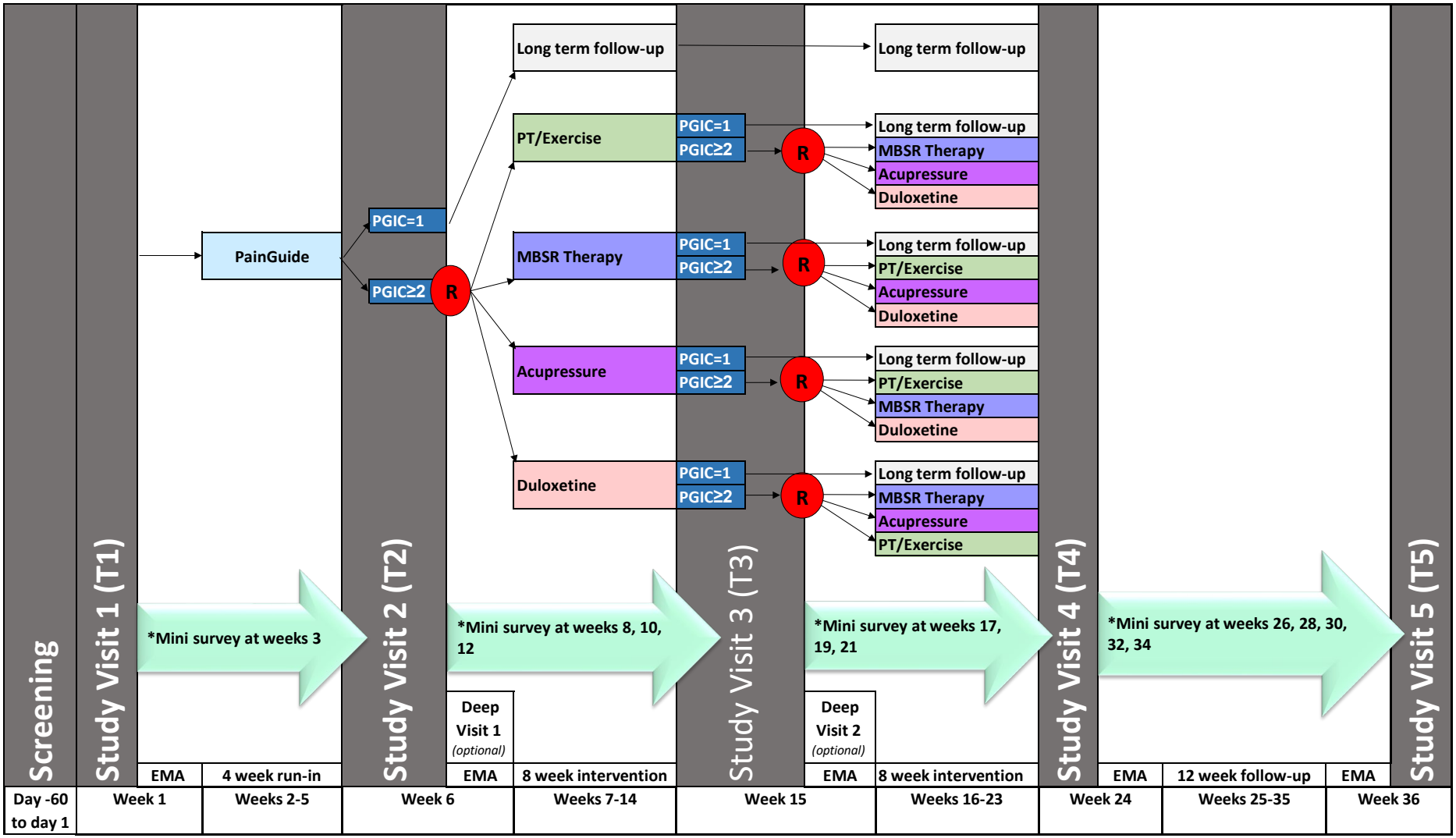
1 Protocol Summary

1.1 Synopsis

Title:	University of Michigan Mechanistic Research Center (BACPAC Study)
Grant Number:	1U19AR076734-01
Study Description:	A long-term pragmatic trial in a cohort of patients with chronic low back pain (cLBP). Using a sequential, multiple assignment, randomized trial (SMART) study design. This will consist of a 4-week run-in period using an online cognitive-behavioral self-management intervention (PainGuide), followed by two 8-week treatment periods. Participants between the ages of 25–70 years old who have cLBP and who are eligible will be followed for approximately nine months. Those who have had minimal or modest improvement in their pain (PGIC≥2) after the PainGuide run-in period will be randomized to one of the four 8-week long interventions. These interventions are Mindfulness-Based Stress Reduction (MBSR), physical therapy (PT) and exercise, acupressure self-management, or duloxetine. After that first 8-week treatment, participants with minimal or modest improvement in their pain (PGIC≥2) will be randomized to a second treatment (one of the three treatments not received before). A subset of participants will complete an additional deep phenotyping assessment.
Objectives*:	Primary Objective: To perform an Interventional Response Phenotyping study in a cohort of cLBP patients. Secondary Objectives: 1. To demonstrate that currently available, clinically-derived measures, can predict differential responsiveness to the above therapies 2. To identify new experimental measures that predict differential responsiveness to each of the above therapies, as well as to infer mechanisms of action of these treatments.
Endpoints*:	1. Primary Endpoint: Pain Change in PROMIS Pain Interference between T2 and T3 study visits 2. Secondary Endpoints: a. Change in the Pain, Enjoyment and General Activity (PEG) Scale between T2 and T3 study visits. b. Change in Patient Global Impression of Change (PGIC) between T2 and T3 study visits
Study Population:	Participants between the ages of 25–70 years old who have cLBP
Description of Sites/Facilities Enrolling Participants:	This study will recruit from 6 outpatient clinics catering to low back pain patients at the Michigan Medicine. There will be no sites outside of the US.
Description of Study Intervention/Experimental Manipulation:	There will be 4 study interventions that participants maybe randomized to in this study. They are: 1. Mindfulness Based Stress Reduction (MBSR): 9 sessions over 8 weeks delivered virtually and in a group setting. 2. Physical Therapy (PT) plus exercise: 10 sessions over 8 weeks delivered individually. 3. Acupressure: self-administered, daily over 8 weeks. 4. Medication- Duloxetine: self-administered medication, daily over 8 weeks.
Study Duration*:	41 months
Participant Duration:	9 months

1.2 Schema



R= Randomization
EMA= Pro-diary wrist device
MBSR=Mindfulness based stress reduction
*=completed remotely online

Figure 1 BACPAC Study Diagram of Study Visits

1.3 Schedule of Activities

Table 1 BACPAC Study- Schedule of Activities and Associated Events

	Scheduled																		Unscheduled Visits	
	Pre-screening (-30days)	Study Visit T1 (Week 1)	Ecological Momentary Activity (EMA)-1 (Week 1)	Study Visit T2 (Week 6)	Deep Visit 1 ≠ (Week 6)	Ecological Momentary Activity (EMA)-2 (Week 6)	Intervention 1 (Weeks 7-14)	Study Visit T3 (Week 15)	Deep Visit 2 ≠ (Week 15)	Ecological Momentary Activity (EMA)-3 (Week 15)	Intervention 2 (Weeks 116-23)	Study Visit T4 (Week 224)	Ecological Momentary Activity (EMA)-4 (Week 24)	Ecological Momentary Activity (EMA)-5 (Week 36)	Study Visit T5 (Week 36)	10 Mini-assessments (Weeks 3, 8, 10, 17, 21, 26, 28, 30, 32, 34)	1 Expanded Mini-assessment (Week 12)	1 Mediation Mini-assessment (Week 19)	Unscheduled Non-study Intervention Triggering Deep	Other Non-Study Intervention Triggering Follow-up Post Treatment (4&8 weeks post
EMR Eligibility Review	x																			
Screening Eligibility Review	x	x																		
Informed Consent		x																		
Charlson Comorbidity Index (CCI)		x																		
Demographics		x																		
Medical History and Medications		x		x				X				x			X					
Vitals, Height & Weight		x		x				X				x			X					
Biomechanical, Physical Exam & Physical Function Measures																				
2-Minute Walk Test (2MWT) 4-Meter Walk Gait Speed Test (from SPPB) Timed Sit-to-Stand (STS)		x		x				X				x			X					
Neurotesting-Patellar Deep Tendon Reflex		x					b				b									

Neurotesting-Achilles Deep Tendon Reflex		x					b				b								
Neurotesting-Sensation		x					b				b								
Neurotesting-Ankle Dorsiflexion (L4)		x					b				b								
Neurotesting-Great toe extension (L5)		x					b				b								
Neurotesting-Hamstrings (S1/S2)		x					b				b								
Neurotesting- Single Leg Calf Raises (S1/S2)		x					b				b								
Neural Tension-Passive Straight Leg Raise + Tightness		x					b				b								
Cross Straight Leg Raise		x					b				b								
SI Provocation-Compression		x					b				b								
SI Provocation-FABER Test		x					b				b								
Fortin Test		x																	
Neurotesting-Hip flexion (L2/L3)							b				b								
Neurotesting-Quadriceps (L3/L4)							b				b								
Neurotesting-Seated Slump Test with Active Straight Leg Raise (ASLR)							b				b								
Neurotesting- Beighton Score (Pinky, Thumb & Elbow)							b				b								
Neurotesting- Beighton Score (Knees & Hands to floor)							b				b								

Hip Abduction-Dynamometer							b				b								
SI Provocation-Distraction							b				b								
SI Provocation-Thigh Thrust							b				b								
SI Provocation-Gaenslen's							b				b								
SI Joint- Active Straight Leg Raise							b				b								
SI Provocation-Sacral Thrust							b				b								
Hip Extension Dynamometer							b				b								
Lumbar Segmental Mobility (PA Spring Test)							b				b								
Prone Instability Test							b				b								
Inclinometer-Flexibility- Flexion, Extension and Side bending							b				b								
Observation for Aberrant Motion							b				b								
Directional Preference-Repeat flexion, extension, side glide							b				b								
Hip Provocation-FADDIR							b				b								
Pain Provocation-Quadrant Test							b				b								
Pheno Device- Motion Assessments & Spine Kinematics Data		x																	
Biospecimen Collection																			
Whole blood *Blood Serum* *RNA PAXgene*		x																	

Saliva																				
Urine Pregnancy Test		x		x	x		x		x		x	x							x	
Imaging- MRI of Back and Pelvis		x																		
Questionnaire Data																				
Pain Duration and Frequency (cLBP)- 2 Items from NIH Research Task Force Minimum Dataset*		x			x				x								x			
Pain location- Radicular Pain Questions Adapted from NIH Research Task Force Minimum Dataset*		x			x				x								x			
Pain Somatization- Abbreviated Pain Somatization Adapted from NIH Research Task Force Minimum Dataset*		x			x				x								x			
Low Back Pain- Specific Pain Intensity*		x		x	x			X	x			x			X	x	x	x	x	x
Opioid use- Single-Item Current Opioid Use*		x		x	x			X	x			x			X		x			
Pain Intensity (PEG)*		x			x				x			x			x		x			
PROMIS Physical Functioning 6b*		x		x	x			X	x			x			X	x	x	x		
PROMIS Anxiety 4a*		x		x	x			X	x			x			X	x	x	x		
PROMIS Depression-4		x		x	x			X	x			x			X	x	x	x		
PROMIS Fatigue		x		x	x			X	x			x			X	x	x	x		
PROMIS Sleep Disturbance 6a*		x		x	x			X	x			x			X	x	x	x		
Sleep Duration*		x		x	x			X	x			x			X	x	x	x		
PROMIS Social Role Activity		x		x				X				x			X	x	x	x		

PROMIS Pain Interference 4a*	x	x		x	x			X	x			x			X	x	x	x	x	x
PROMIS Cognitive Function		x		x	x			X	x			x			X	x	x	x		
PROMIS Pain intensity		x		x	x			X	x			x			X	x	x	x	x	x
Pain Catastrophizing Scale (PCS)*		x		x	x			X	x			x			X		x			
Patient Health Questionnaire-2 (PHQ-2)*		x			x				x								x			
Generalized Anxiety Disorder-2 (GAD-2)*		x			x				x								x			
Patient global impression of change (PGIC)/Global Rating of change (GROC)*				x	x		b	X	x		b	x			X		x		x	x
Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS)*		x			x				x								x			
Fibromyalgia (FM) Survey Criteria 2016 (Widespread Pain Index (WPI) and Symptom Severity Index (SSI))		x		X				X				x			X	x		x		
Widespread Pain*		x			x				x								x			
Life Orientation Test-Revised (LOT-R)		x		x					x				x		X					
Chronic Overlapping Pain Conditions Screener (COPCS)		x			x				x											
Pain Self-efficacy Questionnaire (PSEQ)		x		x				X				x			X					
PainDETECT		x		x	X			X	x			x			X					
Oswestry Disability Scale (ODI)		x		x			b	X			b	x			X					

Chronic Pain Acceptance Questionnaire (CPAQ-8)		x		x			c	X			c	x			X				
Fear Avoidance Beliefs Questionnaire (FABQ+Physical Activity)		x		x				X				x			X		x	x	
Experiences Questionnaire (EQ)-11		x		x				X				x			X		x	x	
Experiences Questionnaire (EQ)-5							c				c								
Perceived Stress Scale (PSS)		x		x				X				x			X				
Positive and Negative Affect Scale (PANAS)		x		x				X				x			X				
Childhood and Recent Traumatic Events Scale (CTES)		x																	
Credibility and Expectancy Questionnaire (CEQ)				x				X				x			X				
Client Satisfaction Questionnaire (CSQ)		x		x				X				x			X				
HEAL Treatment Expectancy v1.0 Short Form 6a		x		x				X				x			X				
Numeric Pain Rating Scale (NPRS)		x	x		x	x	b		x	x	b		x	x					
General Sensory Sensitivity (GSS-8)		x		x	x			X	x			x			X	x	x	x	
Ecological Momentary Activity (EMA) Mental and Physical Symptoms			x			x				x			x	x					
Low-Back Pain Treatment Categories Questionnaire		x		x				X				x					x	x	

Patient Preference Questionnaire		x																	
Patient Outcome Questionnaire		x																	
BACPAC Customer Service Questionnaire								x							x				
Randomization				a				A											
Adverse Event Reporting		x	x	x	x	x	x	X	x	x	x	X	x	x	X	x	x	x	x	x
Deep Phenotyping Participants (n=160)																			
Biospecimen																			
RNA PAXgene					x				x										x	
Blood Serum																			
Whole Blood																			
Neuroimaging- fMRI					x				x										x	
Conditioned Pain Modulation (CPM) Test					x				x										x	
Cuff Ascending and Pseudorandom					x				x										x	
Multimodal Automated Sensory Test (MAST) and Cuff Familiarization					x				x										x	
Multimodal Automated Sensory Test (MAST) Ascending					x				x										x	
Temporal Summation					x				x										x	
Tonic Cuff					x				x										x	
Two Point Discrimination Test (TPDT)					x				x										x	
Visual task					x				x										x	

≠ Only completed for deep phenotyping (n=160) participants

** Part of the HEAL minimum data set*

a Randomization will only occur if PGIC≥2

b Occurs if intervention is Physical Therapy
c Occurs if intervention is MBSR

2 Introduction

2.1 Study Rationale

According to the 2011 Institute of Medicine (IOM) report, chronic pain affects more Americans than coronary heart disease, diabetes and cancer combined at an estimated cost of $635B per year.[1] Low back pain (LBP) is the most common pain complaint in adults, and 70-85% of people will experience back pain at some point in their lifetime. Among people with acute LBP, between 10% and 15% will go on to develop chronic low back pain (cLBP)[2] and this chronicity is associated with higher costs, long term functional impairment, disability and poor quality of life. Concerns about the opioid epidemic, as well as an aging population that boosts the prevalence of cLBP,[3] emphasize the critical need to advance how we conceptualize and treat cLBP.

At present there are data suggesting a variety of structural/mechanical, neural, psychological, cognitive, behavioral, social, and economic factors that contribute to cLBP. Acknowledgement of this complex set of pathogenic factors in the etiology and maintenance of cLBP is referred to as the biopsychosocial model of chronic pain. Not surprisingly, with so many potential contributors to this clinical disorder, inconsistent approaches to diagnosis and treatment has left many patients without adequate pain relief. The BACPAC initiative has chosen to address the many facets of the biopsychosocial model in a comprehensive and unbiased manner and provide an integrated translational approach to identifying both the underlying mechanisms operative in cLBP, as well as the treatments that work on those underlying mechanisms. The UM BACPAC MRC study proposed here will support the overall BACPAC initiative where a vast amount of data will be collected from each participant to better understand who responds to what treatment.

The most widely used treatment options for cLBP typically include a combination of medication and surgical procedures, with the goal of relieving pain and restoring function. Unfortunately, despite advances in pain management, medical interventions alone frequently cannot resolve cLBP, leaving many patients with a significant amount of pain and limited functioning. While medications can be modestly beneficial for some patients with chronic pain,[4-7] behavioral interventions such as cognitive-behavioral therapy (CBT) have demonstrated similar, albeit modest, effects for reducing symptoms.[5,8-11] It is now widely accepted that optimal management for cLBP includes treatments that address not just the biological cause, but also the role of psychosocial factors in the development and maintenance of chronic pain. Given the largely underwhelming effects of current treatments, chronic pain remains a serious public health issue and there must be a cultural transformation in how pain is understood, assessed and treated. One possible explanation for the small effect sizes seen with most of the current treatments for cLBP is that patients are not being adequately matched to appropriate interventions. We hypothesize that an Interventional Response Phenotyping study can identify individuals with different underlying mechanisms for their pain who thus respond differentially to evidence-based interventions for cLBP. To address this hypothesis, we will conduct a sequential, multiple assignment, randomized trial (SMART) for the treatment of cLBP with the following three aims:

Aim 1: To perform an Interventional Response Phenotyping study in a cohort of cLBP patients. We will perform a pragmatic trial using a cohort of cLBP patients, who will receive a sequence of interventions known to be effective in cLBP. For 4 weeks, all cLBP participants will receive a web-based behavioral self-management program for pain. After the four weeks, individuals with significant levels of pain interference will be randomized in a Sequential, Multiple Assessment, Randomized Trial (SMART) to a series of treatments, including: a) mindfulness-based stress reduction (n=110), b) physical therapy and exercise (n=110), c) acupressure self-management (n=110), or d) duloxetine (n=110). After 8 weeks, individuals who remain symptomatic will be re-randomized to a different treatment for an additional 8 weeks.

Aim 2: To demonstrate that currently available, clinically-derived measures, can predict differential responsiveness to the above therapies. We will leverage the above study to perform the most comprehensive study-to-date of currently available predictors for commonly used cLBP therapies. All patients enrolledin Aim 1 will complete baseline clinical phenotyping that will include the following potential predictors of treatment response: a) demographics, b) questionnaires assessing underlying pain mechanisms, c) ambulatory symptom

monitoring, d) extensive psychological assessment using validated patient-reported outcomes, e) structured physical examination, and f) state-of-the-art structural imaging of the back and pelvis.

Aim 3: To identify new experimental measures that predict differential responsiveness to each of the above therapies, as well as to infer mechanisms of action of treatments. A subset of individuals (n=160) from the larger cohort in Aims 1 and 2 will be asked to participate in an expanded phenotyping study that will include structural and functional brain neuroimaging, quantitative sensory testing (QST), plasma measures of inflammation, and digital measurement of autonomic tone.

2.2 Background and Significance

Chronic low back pain (cLBP) affects an estimated 42 million Americans and is associated with greater healthcare utilization, higher rates of unemployment, worse sleep and more depression compared to those without cLBP.[12] At present there are data suggesting a variety of structural/mechanical, neural, psychological, cognitive, behavioral, social, and economic contributors to cLBP. Not surprisingly, with such a disjointed understanding of the causes of cLBP, treatment has suffered, and many individuals fail to get relief from their pain.

Based on our experience with a similar initiative, the MAPP network http://www.mappnetwork.org, which is nearly identical in structure to the proposed BACPAC, one of the issues we addressed as a consortium, was how to determine if any sub-grouping or endophenotype could be clinically meaningful. In other words, would a subset of individuals respond to certain treatments, while another slightly different subset of patients would not. During the process of conducting the MAPP, we were left with mountains of functional neuroimaging, -omics, QST, psychological and other biomarker data on deeply-phenotyped pelvic pain patients, but we still did not know to which treatments each of these participants would or would not respond. We lacked the ability to link endophenotypes or biomarkers to differential responses to treatments - the holy grail of precision medicine. Dr. Clauw helped coin the term ***"interventional response phenotyping"*** to describe the critical need in efforts such as BACPAC to attain high quality information on participants that can predict which non-pharmacological, pharmacological, or procedural therapies they do and do not respond. These studies were incorporated into the second, ongoing phase of the MAPP and a similar approach is proposed here.

To conduct an interventional response phenotyping study, a SMART[13] design was selected. A SMART design involves multiple intervention stages (here two stages will be used) where each participant moves through each stage and can be randomly assigned to an intervention at each stage. SMARTs have been used in many fields,[14] especially in mental health and behavioral interventions.[15-18] To our knowledge, only one SMART has investigated interventions to treat pain; however, it was in the setting of breast cancer and investigated behavioral interventions only.[19]

The proposed SMART is the first to investigate both behavioral and medical interventions in cLBP. While the goal of many SMART designs is to develop effective adaptive interventions[20] or tailored sequences of treatments for individuals, SMART designs may instead be motivated by other goals.[21] The proposed SMART design was motivated both scientifically and from a patient perspective to glean more information from the same participants while exposing them to up to two treatment periods so that if sufficient reduction in pain and interference from pain is not realized after the initial intervention, the participant can receive a different or complementary treatment. The primary goal of the proposed SMART is to uncover the underlying disease mechanisms that are targeted by each intervention. Secondarily, we can also explore the embedded adaptive interventions within the SMART design to provide guidelines over a longer course of treatment for physicians and patients to better treat cLBP at a personalized level. Below is an overview of the study presented in the context of the aims (Figure 2). For Aim 3, a subset of participants will undergo additional assessments (e.g., neuroimaging, quantitative sensory testing) before and after the first treatment (yellow arrows). Another smaller number of participants receiving non-study treatments such as back surgery or injections will also undergo the same additional assessments before receiving the scheduled non-study treatment (red arrow).

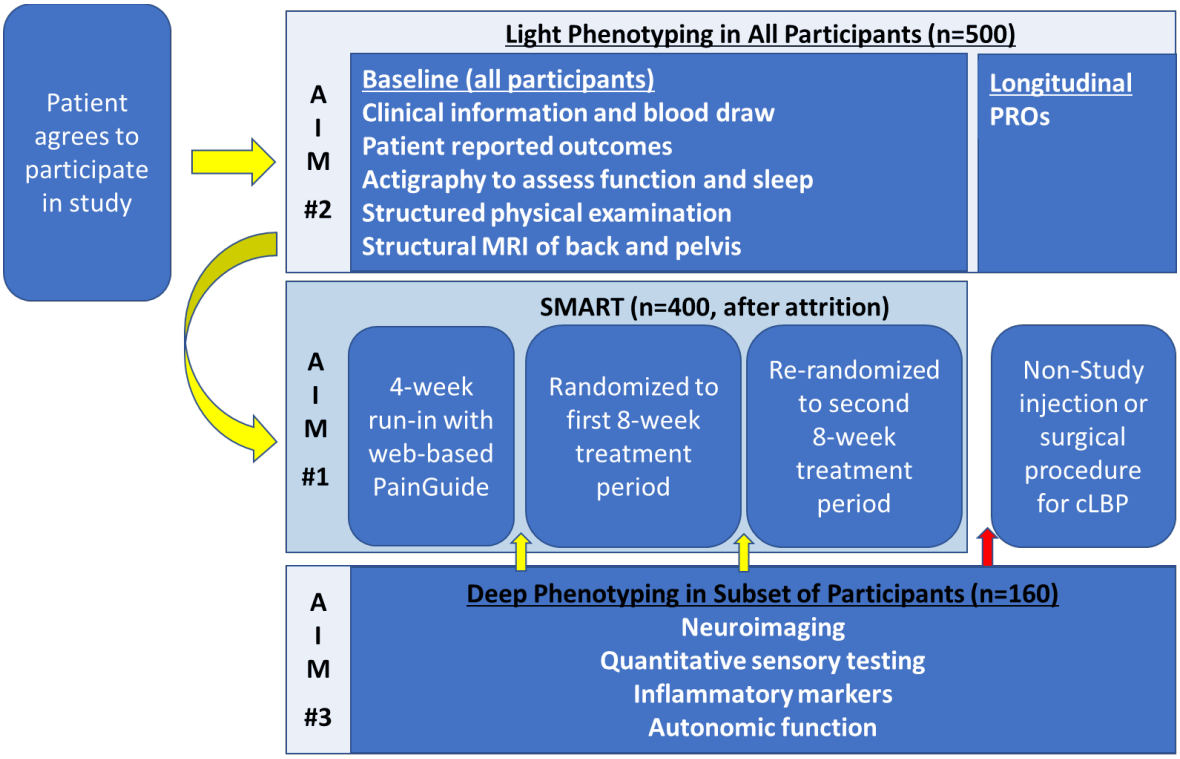


Figure 2 Sequential Multiple Assignment Randomized Trial (SMART) design

The four following treatments were selected as it is presumed that each has a unique mode of delivery and presumed mechanism of action. Each treatment is briefly described below, as are some of the presumed mechanisms underlying effectiveness

2.2.1 Mindfulness-Based Stress Reduction (MBSR)

Mindfulness-based interventions (MBIs) such as mindfulness-based stress reduction (MBSR) are increasingly widely used non-pharmacological interventions for pain reduction involving mindfulness meditation [22-24], and are now recommended in many treatment guidelines for cLBP. MBSR is typically delivered in a group setting with trained providers. Weekly sessions take place over an 8 to 12-week period and require extensive homework for participants. Meta-analyses report that MBIs reduce pain intensity and pain interference in chronic pain syndromes, including cLBP with effect sizes of 0.3-0.5 [24-27], although data quality is yet only fair. MBIs also improve depression, anxiety, and addiction [28-30] that often accompany chronic pain, and have been found to reduce opioid misuse in chronic pain sufferers [31-33]. MBIs train patients to engage dispassionate attention toward the present-moment sensory experience of pain, and to meta-cognitively *observe and disengage* from cognitions, projections, and emotional/distress reactions about one's pain [22,23,34,35]. This is consistent with reports that beliefs, anticipation, and depressive and anxious states can lead to physiological amplification of pain intensity [34-36], and conversely that attentional modulation may alter pain perception [34,36]. Mindfulness increases capacity for meta-cognitive attention/ "decentering" and acceptance, decreases personalization of pain distress, emotional reactivity, rumination, and worry, and improves regulation of distress responses to pain [22,23,37-39] (see meta-analysis [40]), decreases pain catastrophizing [41,42] and increases positive reappraisals.[43] Mindfulness is associated with increased activity in brain circuits involved in sensory perception (e.g. insula and dACC) during laboratory pain [37,44-46], and decreased activity in circuits involved in elaborative and self-related processes (e.g., dlPFC, OFC, vmPFC) during active pain, anticipation of pain, and at rest (see reviews [37,39,47,48] and meta-analyses [49,50]). The pain reduction mechanism of mindfulness appears distinct from placebo and does not involve the endogenous opioid system.[37,51,52]

2.2.2 Physical Therapy and Exercise

Physical therapy (PT) and exercise are amongst the most commonly recommended treatments for cLBP and have a strong evidence base of support. PT consists of a variety of approaches such as manual therapy, directional preference exercises, and nerve mobilization procedures that are tailored to patients based on assessment of their movement characteristics. PT is typically delivered 1:1, in person and by trained physical therapists. PT is supplemented by exercise done outside of the clinic setting that often includes aerobic exercise, stretching and walking.[53] There are few mechanistic studies probing precisely how these treatments exert palliative effects or what type of neurobiological marker would predict treatment responsiveness. A few issues complicate our understanding of the neurobiological mechanisms of action for PT/exercise. The vast majority of cases of back pain (70–80%) do not have a specific cause that can be determined even after thorough examination (Pederson, 2015). In addition, there is a lack of a strong association between pathology and pain in which a proportion of people with back pain have no abnormality found from imaging and others with no pain show abnormalities.[53,54] In addition, exercise has important effects on psychological functioning (anxiety and depression), that may confound a purely neurobiological explanation for how pain is improved by exercise.[55]

2.2.3 Acupressure

Acupuncture is a component of Traditional Chinese Medicine (TCM) wherein thin needles are inserted at specific points on the body (acupoints) to treat disease. Research over the past three decades has shown that acupuncture is effective for the treatment of chronic pain (for recent meta-analysis see[56]). Acupressure is a related technique wherein pressure is applied via a finger or device to specific *acupoints*. Acupressure is highly scalable and can be taught to patients (for self-application) and supported by the use of technology. While less research has been performed on self-applied acupressure, emerging data indicates that self-acupressure is effective for chronic pain[57,58], and low back pain specifically.[59-62] In our own studies, we completed a randomized clinical trial in 288 fatigued breast cancer survivors who self-administered acupressure (as proposed in this application) and found significant improvements in pain, fatigue, sleep, and depression.[63,64] We also recently completed a randomized controlled trial of our acupressure intervention in 67 cLBP patients randomized to either acupressure or usual care. In that pilot study, self-acupressure reduced low back pain more so than usual care (35% reduction, $p<0.05$) after 6 weeks of treatment. These data support the proposal of using self-acupressure as an intervention to treat cLBP.

2.2.4 Non-Opioid Pharmacotherapy

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) that is FDA-approved for use in cLBP,[65-67] and, as such, is included as a recommended therapy in nearly all current treatment guidelines for low back pain. Hence, duloxetine is a logical non-opioid analgesic to include in our SMART trial. Duloxetine and other drugs that increase both serotonergic and noradrenergic activity (e.g. tricyclics) are thought to work as analgesics by increasing activity in down descending anti-nociceptive pathways.[68]

3 Methodology

3.1 Overview of Study Design

We will conduct a long-term pragmatic trial in a cohort of cLBP patients (see Figure 2 above). The proposed SMART will consist of a 4-week run-in period using an online cognitive-behavioral self-management intervention (PainGuide), followed by two 8-week treatment periods. All participants will be followed for approximately nine months. At baseline (T1), all patients will undergo a comprehensive baseline phenotyping assessment. After receiving PainGuide for 4 weeks, all participants will complete a light phenotyping assessment (T2) and a subset of these patients (n=160) will complete an additional deep phenotyping assessment (described in Sections 3.2 and 10). Those who have minimal or modest improvement in their pain (PGIC≥2) will be randomized to one of the four 8-week long interventions (i.e., MBSR, PT/exercise, acupressure, or duloxetine). Following the first 8-week treatment period, patients will be reassessed (T3) using light only or light plus deep assessments (for the subset of 160) and those who have minimal or modest improvement in their pain (PGIC≥2) will be re-randomized to receive one of the three treatments they did not

receive in the first treatment period. After the second intervention and three months later, all undergo the light phenotyping follow-up assessment protocol (T4). Lastly, a final assessment will take place at 3 months after the scheduled end of the second 8-week treatment period (T5). There will also be a series of 12 “mini” assessments that take place at 2-week intervals in between the regular assessments (T1-T5). Primary outcome completion date will be defined as the date of the final collection of data for the primary outcome. For this study, this will be the completion of the PROMIS Pain Interference questionnaire at T3. Study completion date will be the date of the T5 study visit.

3.2 Deep Phenotyping (optional)

A subset of patients (n=160) will undergo “deep” phenotyping, with additional testing such as quantitative sensory testing (QST), functional neuroimaging (fMRI), autonomic nervous system (ANS) function assessment, and collecting additional blood samples for basal and stimulated immune markers. While screening, recruitment, baseline visits and light phenotyping visits will occur at the Back & Pain Center, study visits for deep phenotyping will take place at the Chronic Pain and Fatigue Research Center (CPFRC). The neuroimaging will take place off site at a UM-affiliated location. There will be two deep phenotyping assessments that take place at the CPFRC before and after Treatment 1. Unscheduled deep assessments (described in Section 10.4) will also be offered to patients undergoing medically indicated procedures and interventions for their cLBP that occur outside of this study.

3.3 Proposed SMART Design

We have proposed a Sequential, Multiple Assignment, Randomized Trial (SMART) design (see Figure 2 above).[13,20,69] Individuals will be randomized to one of four treatments, and then following the first treatment period, if they have minimal improvement in pain (PGIC≥2), they will be re-randomized to receive a second treatment.

4 Participants

Individuals who are ages 25-70 years and are being seen at Michigan Medicine will be recruited. Diversity in race and ethnicity will be sought. All races and ethnicities will be considered for inclusion in the study. Randomizedwill be defined as the number of participants enrolled and randomized into the 4 treatment arms. This study will randomize 400 participants (100 into each intervention) and it is expected that600 participants maybe enrolled to meet this goal. Recruitment ends when this randomization goal is met.

There will be two sets of inclusion and exclusion criteria. The first set of criteria is for enrollment into the research project for all participants. The second set represents additional inclusion and exclusion criteria that are necessary for the safe and valid conduct of the deep phenotyping protocol (subset n=160).

4.1 Inclusion Criteria for Light Phenotyping

- We will use the definition of cLBP described in the NIH Task Force Report on Research Standards for Chronic Low Back Pain, i.e., low back pain present at least six months, and present more than half of those days.[70]
- Individuals must have a pain interference score of ≥60 on PROMIS Pain Interference. The normal population mean for pain interference is 50. Participants must be 1 SD above the population mean (>=60) for inclusion.
- Individuals must be willing and eligible to be randomized to receive at least three of the four proposed treatments.

4.2 Exclusion Criteria for Light Phenotyping

- History of discitis osteomyelitis (spine infection) or spine tumor
- History of an autoimmune disorder such as ankylosing spondylitis, rheumatoid arthritis, polymyalgia rheumatica, psoriatic arthritis, or lupus
- History of cauda equina syndrome or spinal radiculopathy with functional motor deficit (strength <4/5 on manual motor testing)

- History of schizophrenia or schizoaffective diagnosis
- Diagnosis of any vertebral fracture in the last 6 months
- Osteoporosis requiring treatment other than vitamin D and calcium supplements
- Cancer
    - History of any bone-related cancer or cancer that metastasized to the bone
    - Currently in treatment for any cancer or plan to start cancer treatment in the next 12 months
    - History of any cancer treatment in the last 24 months
- Life expectancy less than 2 years
- Unable to speak and write English
- Visual or hearing difficulties that would preclude participation
- Uncontrolled drug/alcohol addiction
- Individuals started receiving disability or compensation within the past year, or currently involved in litigation
- Pregnancy or breastfeeding
- Individuals on high doses of opioids (over 100 OME per day)
- Scheduled back surgery, back surgery within the last year, or more than one back surgery in the past.
- Expecting to receive an injection of surgical procedure within the next year for their cLBP
- Current/planned (in the next 2 years) enrollment in another study of a device or investigational drug that would interfere with this study, this may include participation in a blinded trial.
- Any other diseases or conditions that would make a patient unsuitable for study participation as determined by the site principal investigators. This would include but not be limited to severe psychiatric disorders, active suicidal ideations or history of suicide attempts, and an uncontrolled drug and/or alcohol addiction)

4.3 Contraindication to study interventions

4.3.1 Duloxetine

- Contraindications to receiving duloxetine:
    - Medications such as:
        - Lithium
        - Tramadol (Ultram, Ultracet)
        - St. John's Wort
        - Prochlorperazine (Compazine)
        - Thioridizine (a psychiatric medication)
        - Propafenone or Flecanide (for heart rhythm problems)
        - Ciprofloxacin (Cipro, an antibiotic)
        - Linezolid (Zyvox, an antibiotic)
        - Methylene Blue
        - Cimetidine (Tagamet, for heartburn)
        - Clomipramine (Anafranil)
        - Vortioxetine (Trintellix)
        - SSRIs:
            - sertraline
            - paroxetine
            - fluoxetine
            - escitalopram
            - citalopram
            - fluvoxamine
        - SNRIs:
            - Venlaxaxine
            - Milnacipran

- Duloxetine
- Sibutramine
- Atomoxetine
- Desvenlafaxine
- Levomilnacipran

  - Renal dysfunction: Creatinine Clearance <30mL/min or End-Stage Renal Failure
  - Hepatic dysfunction: Liver function tests (LFTs) elevated times 1.5
  - History of allergy to duloxetine
  - History of bipolar disorder

4.3.2 Acupressure

- Currently receiving acupressure or acupuncture through a formal therapy

4.3.3 MBSR

- Current participation in a structured MBSR program

4.3.4 Physical Therapy & Exercise

- Currently receiving any type of structured manual therapy or exercise treatment for low-back pain.
- Contraindication for manual therapy and/or participation in an exercise program

4.4 Contraindication to MRI

- Presence of any history that would preclude scanning in MRI (i.e. known metal foreign objects or implants, history of claustrophobia)

4.5 Inclusion Criteria for Deep Phenotyping

- Right hand dominant (such as the hand used when writing or throwing/catching a ball)
- Normal visual acuity or correctable (with corrective lenses- glasses or contacts) to at least 20/40 for reading instructions in the MRI and visual sensitivity testing
- No contraindications to MRI (e.g., metal implants)
- Willingness to refrain from taking any “as needed” medications, including pain medications such as NSAIDs (e.g., Motrin, Advil, Aleve), acetaminophen (e.g., Tylenol), and opioids, for 8 hours before undergoing neuroimaging and QST
- Willingness to refrain from alcohol and nicotine on the day of QST and neuroimaging (alcohol and nicotine consumption is allowed after testing is completed)
- Willingness to refrain from any unusual physical activity or exercise that would cause muscle and/or joint soreness for 48 hours prior to testing (routine exercise or activity that does not lead to soreness is acceptable)
- Able to lie still on their back for 2 hours during MRI

4.6 Exclusion Criteria for Deep Phenotyping

- Severe claustrophobia precluding MRI and evoked pain testing during scanning
- Diagnosed peripheral neuropathy
- Current, recent (within the last 6 months), or habitual use of artificial nails or nail enhancements. (Artificial nails can influence pressure pain sensitivity at the thumbnail)
- BMI > 45 or unable to comfortably fit in the bore of the MRI magnet

4.7 Inclusion Criteria for Pheno Device

- Able to stand for at least 10 minutes

4.8 Exclusion Criteria for Pheno Device

- Known pregnancy
- Blind or severe uncorrected vision problems that prevent participant from reading a tablet or laptop screen

- Deaf or hearing problems that prevent the participant from hearing verbal instructions
- Current low back pain is the result of a traumatic injury (wreck, fall, etc.) that occurred within the last 3 months OR is positive for spine instability with imaging
- Has spinal fusion across 4 or more lumbar disc levels.
- Actively being treated by a medical provider for concussion
- Known severe spinal deformity requiring medical treatment (e.g. scoliosis)
- Has been diagnosed by a medical provider with severe vertigo, fainting, narcolepsy, or balance disorders with high risk for falling
- Any known fractures within the last 3 months that will interfere with the motion assessment
- Any known spine fractures within the last 6 months
- Known unstable spondylolisthesis (i.e. standing 3mm of movement on flexion/extension film)
- Current condition requiring immobilization of the spine
- History of brain or spine cancer
- Currently or within the last 90 days, been treated for any cancer with chemotherapy or radiation therapy
- Known severe osteoporosis requiring medical treatment and physician-recommended physical restrictions
- Current open wounds or medical device entry points where the harnesses will be placed on the back or hips
- Current osteomyelitis or spine infection
- Any other reason that a treating physician, researcher, or participant determines it is unsafe for a patient to perform test

5 Recruitment

We will enroll adults meeting the inclusion and exclusion criteria from Michigan Medicine outpatient clinics such as the Back & Pain Center and satellite clinical sites, as well as the UM Physical Medicine, Family Medicine, and Neurosurgery clinical sites. Patients will also be recruited through online platforms such as Facebook, back pain forums and umhealthresearch.org, through health fairs and passively with study flyers and advertisements, such as bus ads, radio, and online news platforms (ie. MLive). Additionally, eligible patients may be identified using the Back & Pain Center new patient database known as APOLO (HUM00041820) and by using Data Direct queries. Patients will be contacted by phone or in person and screened using study screening forms. Interested and eligible patients will then be scheduled for an in-person baseline study visit at the Back & Pain Center or seen virtually for a similar visit. Follow-up study visits maybe a hybrid of in-person and virtual to limit time in clinic and decrease participant burden. Potential subjects who have been screened for study participation and were not enrolled for the study will be considered screen failures. Primary reasons for screen failures will include inclusion/exclusion criteria not met, lost to follow up, and withdrawal from study. Screen failures will be reported electronically and reminders will be scheduled for re-screening in 3 months depending on the conditions of the screen failure.

6 Baseline Visit

All baseline visits will take place at the Back & Pain Center. Step one will consist of the informed consent process conducted by trained study staff. This will be followed by questionnaire completion using Qualtrics electronic data capture system, physical function testing, structured physical exam, a blood draw and orientation to the ambulatory symptom monitoring devices (PRO-diary). Participants will also undergo an MRI of the back and pelvis at a later that day or on another day. The elements of the baseline assessment are described below.

6.1 Study Questionnaires

All data collected on study participants will be obtained and managed for research purposes. The types of data to be collected are self-report questionnaires that assess the following: demographic characteristics,

diagnostics, physical and psychological symptoms, life functioning, opioid use, other ongoing treatments, and treatment expectancies, use, and satisfaction.

Study surveys will be completed using Qualtrics electronic data capture system. Paper versions will be made available but use of the electronic data capturing system is preferred. The patient's own entry of responses will serve as the source record. Participants will complete electronic assessments at study visits (T1-T5)- baseline, before Treatment 1, after Treatment 1, after Treatment 2 and 12 weeks after completion of Treatment 2. Participants will also complete 12 online mini-assessment (described in Section 12.1) every two-weeks throughout the course of the study. Study surveys, including the collection of the HEAL Minimum Dataset, are described in Section 1.3.

6.2 Clinical Data and Medical History

At every visit medical history will be collected and reviewed from the participant. Medications (especially analgesics including opioids), medical diagnoses, family history, surgical history and other treatments reported will be confirmed via EMR review. At every in-person assessment visit, clinical data will be collected on each participant including weight and height, waist and hip ratio, blood pressure, heart rate, temperature, and pregnancy status (urine pregnancy test if potentially pregnant [premenopausal, ambiguous last menstrual period, intact reproductive system]). Comorbidities will be assessed using the Charlson Comorbidity Index (CCI) and EMR review. If the visit is conducted virtually, clinical data such as blood pressure, will be collected from their most recent in person visit.

6.3 Physical Exam

The clinical exam will be conducted by study-related physicians or a trained member of the research team and consist of a series of assessments that are routinely used in the care of patients with cLBP. Elements of the physical exam and the pain problem that they are directed to evaluate are described in Section 1.3.

6.4 Physical Function Performance Tests

Three performance tests are included in the baseline phenotyping. The first two performance tests come from the NIH Toolbox measures of motor function, a group of validated assessments that have robust psychometric properties and scoring features[71]. The first test is the 2-Minute Walk Endurance Test. This test is adapted from the American Thoracic Society's 6-Minute Walk Test Protocol[72]. Participants walk their usual pace for 2 minutes on a 50-foot (out and back) course while being timed. The participant's raw score is the distance in feet and inches walked in 2 minutes. The test takes approximately 4 minutes to administer. The second test is the 4-Meter Walk Gait Speed Test. This test is adapted from the 4-meter walk test in the Short Physical Performance Battery[73]. Participants are asked to walk 4 meters at their usual pace. Participants complete one practice and then 2 timed trials. Raw scores are recorded as the time in seconds required to walk 4 meters on each of the two trials, with the better trial used for scoring. This test takes approximately 3 minutes to administer. These tests are particularly appropriate for people with cLBP because walking speed and endurance is affected not only by pain, but also by sedentary behavior and obesity,[74] which are common in people with cLBP. The final test is the Five Time Sit to Stand Test[75] which is a valid, reliable measure of physical disability in people with cLBP.[76,77] In patients with cLBP, the change of position from sit to stand is a good test of how pain affects physical movement and taps a slightly different physical domain than the NIH Toolbox motor assessments. Patients are instructed to stand up 5 times from a chair with their arms folded across their chest as fast as possible while being timed. Inability to rise from a chair five times in less than 13.6 seconds is associated with increased disability. [75]

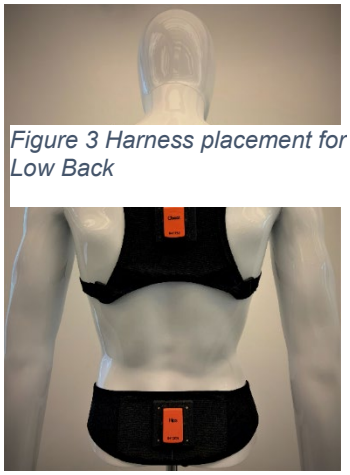


Figure 3 Harness placement for Low Back

6.5 Biomechanical Data Collection

Biomechanical data will be collected using the Pheno device during the baseline study visit (T1). Research personnel will be trained on using all study device

equipment. Additionally, participants will be asked additional screening questions to ensure it is safe to use the Pheno device (see Sections 4.5 and 4.6).

Instructions will ask participants to perform the motions as fast or as far as they can comfortably to avoid above risks. Digital data will be stored in our custom software application on the OSU Amazon Web Services (AWS) server, which is equipped to handle PHI and compliant with 21 CFR Part 11 for electronic records.

6.5.1 Pheno Hardware

Motion assessments performed in Pheno use commercially available IMU sensors (XSens MTw2) that are designed specifically for collecting human kinematics non-invasively. They are powered by very small batteries (similar to those found in commercial activity monitors or smart watches) and do not pose significant electrical discharge risk. Additionally, they are sweat resistant as they are fully sealed except for a small micro-USB charging port.

Though designed for safe human contact, these sensors do not touch our participants in our application as they are mounted on a series of custom harnesses which provide additional insulation. Harnesses will be worn over clothing. Harnesses were designed to be extremely light (a few ounces each), comfortable, and non-intrusive for nearly any body style. All materials are non-abrasive (no exposed velcro, sharp edges, etc.), easy to wipe down with alcohol wipes, non-allergenic (e.g. no latex), and highly flexible. Subjects typically only wear the system for a few minutes at a time so there is minimal risk for long-term discomfort.

6.5.2 Spine Kinematics Data

Kinematic spine data will be captured from the Pheno device mentioned above. Additional kinematic data will be collected from a markered optical motion capture system for a subset of subjects who are able to participate at a location that includes these capabilities. Markered optical motion capture systems use a series of near-infrared cameras to track small reflective markers placed on the harnesses that the participant is already wearing (Figure 4). Though safe for human contact, these reflective markers do not come in contact with the participant in our particular application. Data captured from cameras is non-identifying and primarily includes x-y location of each reflective marker. The inclusion of this additional instrument does not affect subject risk in any way.

Figure 4 Reflective markers (silver dots) that are added to harnesses when using markered optical motion capture system

Inertial and optical motion tracking systems have been used for several years to quantify biomechanical motion in athletes, patients, and workers and are the standard for safely capturing quality kinematic data in this industry.

6.6 Biospecimens

Blood serum, whole blood, urine, and saliva may be collected as part of the global BACPAC phenotyping effort that includes DNA, transcriptomics, proteomics, and other “omic” analyses. Participants will rest quietly for several minutes prior to venipuncture. A maximum of 20ml of blood will be drawn from either arm. Samples will be labeled with coded subject ID numbers. Biospecimens will only be collected at the baseline (T1 visits) for light phenotyping and urine for pregnancy testing, when applicable, will be collected at all 5 time points (T1-T5). All samples will be stored initially at the University of Michigan and may be sent to other MRCs or central biorepositories for future storage or additional analyses. Biospecimen collection for deep phenotyping is described in Section 10.3.

6.6.1 Whole blood

Whole blood will be drawn into PAXgene whole blood RNA tubes (<10mL). The tube is inverted 8-10 times and then stored at room temperature for two hours. Samples are then placed in a -80^0 C freezer (or -20^o C for up to 24 hours) for batch analysis.

6.6.2 Blood Serum

Up to 15mL of blood will be drawn into "red top" containers for the collection of blood serum. Samples are allowed to clot on ice for 15-30 minutes and then centrifuged for 10-20 minutes at 1000-2000rcf for the isolation of serum. Serum is subsequently aliquoted into .5-2mL containers and stored at -80^0 C for batch analysis of proteins (e.g., proteomics).

6.6.3 Urine

Urine is collected in standard collection cup by the and will only be used for urine pregnancy test at T1-T4.

6.6.4 Saliva

Approximately 2mL of saliva is collected in supplied container (e.g., Oragene, DNA Genotek) and stored at room temperature until transfer to -20 or -80^0 C for future whole genome sequencing.

6.7 Structural MRI of the Back and Pelvis

Patients will be scanned on a 3T Philips magnet at the main hospital on the Michigan Medicine campus (Department of Radiology, MRI Facility on B2-Level, UH B2B405, 1500 E. Medical Center Dr., Ann Arbor, MI 48109). A routine lumbar spine protocol (sagittal T1, sagittal T2 with and without fat saturation, axial T2 in one or two blocks) will be used. This follows the consensus statement from the ACR-ASNR-SCBT-MR-SSR practice parameter guideline for spine scanning. Optional Coronal T1 will be obtained to include sacroiliac joints since SI-joint pain is a confounder in back pain evaluation. A volumetric sagittal T2 will be obtained if time permits, this will allow for broader application between our site and University of California-San Francisco (UCSF). Lastly, if time permits, a routine axial T1 may also be obtained for muscle bulk evaluation. Images will be interpreted by Remy Lobo, MD, (board certified radiologist with a CAQ in neuroradiology).

Degenerative changes will be scored according to an MRI scoring sheet was developed by UCSF U19 REACH. Scoring of the MRI will include the following; a) BMIC (Bone Marrow Intensity Changes or Modic Changes), b) Endplate defects, c) Disc Quality, d) Facet Joints, e) Stenosis.

6.8 Actigraphy and Ecological Momentary Assessment (EMA)

After completing the screening/baseline activities, participants will receive instruction on the use of the PRO-Diary monitor, which the participant will wear during 5 separate 7-day "home monitoring" periods, at baseline (sent home with watch following baseline visit) and T2-T5 to assess physical activity (objectively measured via accelerometry), and ecological momentary assessment (EMA) of mental and physical symptoms. EMA will be collected during Weeks 1, 6, 15, 24 and 36).

Figure 5 Pro-Diary- a wrist accelerometer

To measure real-time physical activity and collect ecological momentary assessment data, we will utilize the PRO-Diary (Figure 5 http://www.camntech.com/products/pro-diary/pro-diary-overview), a wrist-worn accelerometer with a touch-screen user-interface. The PRO-Diary collects physical activity data (via a triaxial MEMS accelerometer) as 'activity counts' during regular epochs during the home monitoring period and stores time-stamped self-report data until the participant returns the watch to the lab, where the data will be downloaded for cleaning and analysis.

EMA data will be collected using a wrist-worn PRO-Diary or by distributing surveys via text message through Qualtrics. EMA ratings at wake and bedtime will be initiated by the participant upon waking (not necessarily when they get out of bed) and at bedtime ("lights out" or the time they intend to go to sleep, not necessarily the

time they get into bed). An audible alert (beep) or vibration will alert participants to enter midday ratings; the PRO-Diary will be programmed to deliver the alert at a random time each day between 11:00AM and 3:00PM. The PRO-Diary will display a reminder message to complete bedtime ratings at 8:00PM each day.

6.8.1 Physical activity

The PRO-Diary will collect physical activity data as 'activity counts' during regular 15-second epochs at a sampling rate of 50 Hz[76] during the home monitoring period and store time-stamped self-report data until the participant returns the device back to the lab, where the data can be downloaded for cleaning and analysis. The home monitoring period is 7 days which is recommended to obtain a habitual activity profile and will help control for missing data as literature supports a minimum of 5 days of data needed for valid physical activity measurement in adults.[77] We will require 10 hours of data/day to be considered valid per recommended guidelines.[78] Activity counts per minute will be aggregated using custom-set intervals surrounding the EMA ratings. Specifically, these activity counts will be averaged in windows around each EMA rating to provide an estimate of activity that was relatively concurrent with the ratings. This will allow for examination of pain intensity and interference in the context of changes in physical activity. Average activity counts per minute for the entire assessment period will also be calculated to assess overall pre- to post-treatment changes in physical activity. Other physical activity variables that will be generated in aggregate with EMA and over the whole assessment period include: percent time immobile (an index of sedentary behavior) and maximum activity counts (an index of top physical activity intensity).

6.8.2 Sleep Features

Participants will be asked to enter their "to bed" and "wake" times into the PRO-Diary to demarcate wake and sleep time and aid in calculating sleep features. Sleep variables are computed with onboard software, using measurement of nighttime physical activity, assessed in 15 second epochs. Four sleep variables will be examined in this study, which are commonly measured sleep dimensions in studies using accelerometers.[79] Sleep duration (Total Sleep Time) is the time, in minutes, the individual was asleep. Sleep onset latency (SOL) is the time, in minutes, it takes for an individual to go from a wake state to sleeping. Sleep efficiency (SE) is the percentage of time spent asleep relative to total time spent in bed. Wake after sleep onset (WASO) is the time spent awake in bed after initially falling asleep.

7 PainGuide Run-In Period

After the baseline visit, all participants will be assigned to a web-based behaviorally oriented pain self-management program known as PainGuide (https://bacpac.painguide.med.umich.edu/). PainGuide is an online or smartphone accessible website containing education and evidence-based self-management modules for pain. PainGuide offers (a) education about pain, pain mechanisms, types of pain including cLBP, and education about a wide variety of professionally administered pain treatments; (b) a rationale and resources for using a variety of self-management approaches for pain; (c) a system for online monitoring of symptoms and self-management activities; and (d) external resources (e.g., current literature, patient advocacy groups) that can support the use of self-management. Multi-media is used in communicating content including: videos, text, audio files, and embedded apps. PainGuide is based upon FibroGuide, a similar website for Fibromyalgia which already possesses UM IRB approval HUM00124722 PainGuide can currently be accessed on its development server at the following link. Development server: https://painguide.netlify.app/

During the baseline visit, participants will be supplied a link for obtaining access to PainGuide. Study staff will help orient the participant to the navigation of the site and will aid with login, password creation, and instruct participants to watch the overview sections on chronic low back pain and the rationale for self-management of pain. Study participants will be encouraged to use this program for a period of four weeks with no specific instructions about how often to visit the site or what to do once there. Participants will continue to have access to PainGuide throughout the trial. Use of the website will be captured passively with website utilization metrics. If study participants lack access to mobile devices or computers, a Kindle device will be lent to them for use during the study.

8 Randomization

Blocked randomization will be used for the randomization schedule. Patients will be assigned to MBSR (n=110), PT and exercise (n=110), acupressure self-management (n=110), or duloxetine (n=110). Participants will be recruited and randomized until all 4 arms of the study have been filled, which will require the recruitment of as many as 500-600 participants given that we anticipate that 10-20% will respond to the PainGuide self-management intervention, withdraw or be lost to follow-up.

8.1 Criteria for randomization

Randomization will occur at T2 and T3 study visits. Participants with minimal or modest improvement in pain after the PainGuide run-in (PGIC≥2) will be randomized. Participants who have a robust improvement in their pain (PGIC<2) will not be randomized to treatment. These non-randomized participants will still complete the remaining study visits and mini-assessments. In order to assign equal numbers of participants to each of the 4 study interventions, randomization probabilities will account for the fact that certain participants, e.g. because of a contraindication, may be eligible for only 3 of the 4 treatments.

8.2 Randomization method

We will perform randomization using a randomization software or a randomization list created by a statistician to assign participants to a treatment in an unbiased manner. A biostatistician will develop the randomization plan and will create the un-blinded randomization list to be uploaded to the software This will enable study personnel to obtain treatment allocations and will provide functionality to manage the treatment allocation process. Furthermore, this enables study team members to maintain identifying information from participants. Study staff are not blinded to group assignment. The data analytic team are will get a coded data set and will be able to see interventions assigned to each coded participant. The data analytic team are not part of the clinical research staff and only provide data analysis. The randomization software will also track study treatment-allocation progress and provide documentation of the treatment assignment.

9 Intervention Procedures

After completing the PainGuide run-in period, participants will be assessed using either the light or light plus deep phenotyping assessment battery and those who minimal or modest improvement in their pain (PGIC≥2) will be randomized to one of four 8-week treatments. The treatments will be: a) MBSR, b) PT and exercise, c) acupressure self-management, and d) duloxetine. Following the first 8-week treatment period, individuals will be assessed again using either the light or light plus deep phenotyping battery and those who minimal or modest improvement in their pain (PGIC≥2) will be re-randomized to receive one of the treatments they did not receive in the first treatment period.

9.1 Mindfulness-Based Stress Reduction (MBSR)

Participants randomized to MBSR will meet for 8 weekly 2-hour group sessions and one 6-hour “retreat” with a masters-level or higher therapist formally trained in MBSR (with minimum of MBSR “teacher qualification” by UCSD Center for Mindfulness or equivalent) and with experience working with chronic pain patients. MBSR for pain is manualized and includes all the components of standard MBSR [23,80,81] and exercises for enhancing sensory, interoceptive, and proprioceptive attention and meta-cognitive present-moment awareness with a compassionate, non-judgmental stance. In-session exercises include the raisin exercise, body scan, and sitting mindfulness meditation on the breath, sensations, emotional states, and thoughts. Each session includes practicing formal mindfulness exercises, dialogue and “mindful inquiry” with the therapist and group, and a series of didactic instructions on stress and pain physiology and psychology and using mindfulness for coping with stress and pain in daily life. Patients are asked to practice daily formal mindfulness at home using assigned audio recordings of 30-45-min guided mindfulness exercises (i.e., body scan, mindful movement, stretching/gentle yoga, and sitting meditation) streamed from a patient-specific study link through a platform like Qualtrics. MBSR therapists will be supervised by co-investigator Dr. King. All visits will take place at the Domino Farms, Burlington building Back & Pain Center or the CPFRC or virtually on a HIPAA compliant virtual

platform like Zoom. Table 3 below describes the frequency of surveys and communications to the participants during the MBSR intervention.

Table 2 Schedule of Activities for the MBSR intervention

Session	Intervention	Outcomes measured
1	Introducing Mindfulness Meditation: Doing to Being	
2	Perception & Knowing Are Different	Chronic Pain Acceptance Questionnaire (CPAQr-8) & Experiences Questionnaire (EQ-4)
3	There is Pleasure & Power in Being Present	
4	Stress Reactivity	Chronic Pain Acceptance Questionnaire (CPAQr-8) & Experiences Questionnaire (EQ-4)
5	Stress, Mindful Awareness & Responding	
6	Stressful Communications	Chronic Pain Acceptance Questionnaire (CPAQr-8) & Experiences Questionnaire (EQ-4)
7	How Do I Best Take Care of Myself?	
8	Endings Are Beginnings	
6-hour mini retreat	Occurs between weeks 5-7	

9.1.1 Participant Adherence- MBSR

Participants will also be asked to keep a log of study related activities completed at home. Attendance will be taken at each MBSR session. A check in call will be made by the study team 48 hours after starting the treatment to address any patient questions or concerns. Patient homework adherence can be estimated by download count of each mp3 on streaming site.

9.1.2 Standardizing Assessment and Intervention- MBSR

Delivery of the intervention will be facilitated by in-session therapist checklists. All sessions will be audiotaped, and 20% will be observed and scored for adherence and fidelity.[82]

9.2 Physical Therapy and Exercise (PT)

Participants randomized to PT will meet with the physical therapist twice a week for a 1-hour session for weeks 1 and 2 and then weekly for the remaining 6 weeks (Table 3). For more details, see Physical Therapy Manual. After taking a thorough history, an examination is performed. This examination includes self-reported pain severity and disability as well as clinical assessment such as valuation of strength/endurance, neural mobility, range of motion of the spine and hips, mobility of vertebral segments, and movement patterns that are difficult or avoided (i.e., directional preference). The physical therapist will tailor a program to the participant's needs according to recommended PT practice guidelines that will include in-person treatment, home exercise prescription, and encouragement of progressive, low-intensity, submaximal fitness and endurance activities, such as walking.[53,83] The in-person treatment focuses on three main areas: mobilization (i.e., gaining joint mobility), flexibility (soft tissue and neural mobility), and strengthening (see supporting documents for PT Treatment Manual). Manual therapy is a main treatment component, and exercises include repeated directional preference movements, trunk flexion and stabilization. Exercises address both specific deficiencies noted in evaluation, as well as coordination of body motions. Participants are will be given a home program of exercises to be done daily and asked to engage in daily walking with a set goal based on the individual's capacity and current fitness level. Walking was selected as the aerobic exercise of focus for this treatment because it is recommended for patients with all levels of pain severity, is highly feasible to complete, and has

shown effects on outcomes such as pain and disability.[84,85] At weekly visits with the physical therapist, participants will discuss progress toward meeting their walking goal and adherence to the home exercise program. Based upon the progress, the PT will make any necessary modifications (such as increasing the walking goal, adding or refining home exercises). All visits will occur at the Burlington building, 325 E. Eisenhower Ann Arbor, MI 48108.

Table 3 Schedule of Activities for the Physical Therapy & Exercise Intervention

Sessions (week)	Aerobic Warm Up	Manual Therapy	Mobility	Questionnaires
1&2 (week 1)	5 minutes	None	Directional preference	Oswestry Disability Index (ODI) (*session 1 only*) Numeric Pain Rating Scale (NPRS)
3&4 (week 2)	5 minutes	No more than 15 minutes	Continue directional preference and add hip stretches as indicated	Numeric Pain Rating Scale (NPRS)
5 (week 3)	5 minutes	No more than 15 minutes	Same as previous visit	Numeric Pain Rating Scale (NPRS)
6 (week 4)	5 minutes	No more than 15 minutes	Same as previous visit	Patient global impression of change (PGIC) and Oswestry Disability Index (ODI) and Numeric Pain Rating Scale (NPRS)
7 (week 5)	5 minutes	No more than 15 minutes	Same as previous visit	Numeric Pain Rating Scale (NPRS)
8 (week 6)	5 minutes	No more than 15 minutes	Same as previous visit	Numeric Pain Rating Scale (NPRS)
9 (week 7)	5 minutes	As indicated	No more than 5 min	Numeric Pain Rating Scale (NPRS)
10 (week 8)	5 minutes	As indicated	No more than 5 min	Numeric Pain Rating Scale (NPRS), Patient global impression of change (PGIC) and Oswestry Disability Index (ODI)

9.2.1 Participant Adherence- PT and Exercise

Participants will be asked to keep a log of the home exercises they are able to complete and the time spent on each activity. Attendance for the scheduled PT sessions will also be recorded. A check in call will be made by the study team 48 hours after starting the treatment to address any patient questions or concerns.

9.2.2 Standardizing Assessment and Intervention- Physical Therapy and Exercise

9.2.2.1 Standardizing Examination

Baseline examination will be performed by a physical therapist investigative team. These assessors will go through a two-hour training session to standardize examination procedures. During training, special tests will be reviewed in order to ensure correct performance of measures. Assessors will also review inclusion and exclusion criteria. A checklist will be provided in the standardized examination template to ensure that participants meet eligibility requirements. Fidelity checks will be completed on a semi-annual basis.

9.2.2.2 Intervention Training

Study faculty and residents currently enrolled in or recently graduated from the Michigan Medicine - University of Michigan Orthopedic Residency Program will provide all intervention. Within the curriculum, residents

receive detailed, standardized instruction on research methods and intervention techniques. Residents who will be providing intervention will undergo an additional two-hour training and follow the BACPAC PT training manual (see supporting documents). The program director, Laura Fischer, will provide coverage of care as needed and oversee intervention training. All residents will receive PEERRS training and be added to the IRB.

9.3 Acupressure

The self-acupressure intervention will be delivered using the modified MeTime Acupressure mobile app in addition to in-person instruction via study staff. The MeTime Acupressure app was developed in association with patient focus groups (six focus groups each of eight to ten women) and the University of Michigan 3D Media Laboratory (screen shot examples in Figure 7). The MeTime Acupressure app will be loaded onto computer tablets or smart phones by the participants. Participants will also receive an AcuWand to be used in association with the acupressure app to help participants apply the correct amount of pressure to acupoints (See Figure 6). The self-acupressure intervention points will consist of *Du 20*, Conception Vessel 6 (CV- 6), Large Intestine 4 (LI-4), Stomach 36 (ST-36), Spleen 6 (SP-6), and Kidney 3 (K-3) (See Figure 8). Points will be administered bilaterally except for *Du 20*, and CV-6, which were done centrally.

Figure 7 Sample MeTime Acupressure App

Figure 6 AcuWand Device

Participants will be introduced to the MeTime App and AcuWand device at their clinic visit. A research team member will provide the patient with instructions and guide the patient through using the app, the AcuWand and performing Self-Acupressure. Study participants will be told to perform acupressure once per day and to stimulate each point a circular motion for three minutes. There are 9 acupressure points, totaling 27 minutes of stimulation per day.

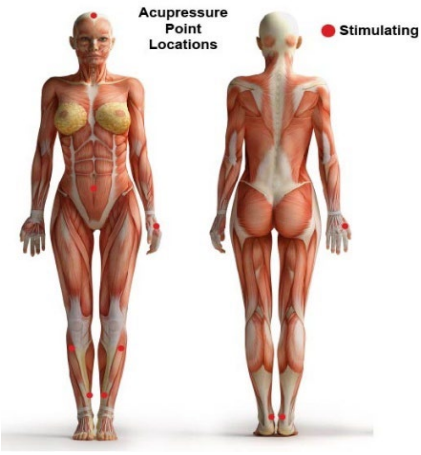


Figure 8 Location of Acupressure Points

9.3.1 Participant Adherence- Acupressure

Participants will be asked to log time spent using the AcuWand on a daily basis and record any reasons for missed sessions. The Acuwand device also records the time a participant spends using the device. A check in call will be made by the study team 48 hours after starting the treatment to address any patient questions or concerns. An additional call with be made two weeks after start of treatment to assess adherence. Text messages remind participants to charge the AcuWand device will be sent at week 4 and 6 of treatment.

9.3.2 Standardizing Assessment and Intervention

Fidelity of the acupressure intervention in study staff, who are teaching participants acupressure, i.e., acupressure educators will be assessed by study investigator Rick Harris every six months. Educators will be trained using the BACPAC Acupressure Therapist Treatment Manual (see supporting documents).

9.4 Duloxetine

All study activities for this arm will take place at the Back & Pain Center, Department of Anesthesiology, at the Burlington Building in Ann Arbor or on a HIPAA compliant virtual platform like Zoom. Participants randomized

to the duloxetine arm will review the dosing schedule for the medication and safety information for the medication at the pre-intervention visit (T2 for Treatment 1 or T3 for Treatment 2) with the study coordinator. At the baseline visits a physical exam was performed by a physician and drug contraindications will be reviewed as an additional precautionary measure.

Participants will then be given 105 pills of 30mg duloxetine with an 8-week dose escalation schedule and an additional 11 pills for those who would like to taper. Participants will be asked to start taking the medication from home, 7 days after the pre-intervention visit (T2/T3 visit). In the event of a shutdown due to COVID, participants may be mailed the study medications by the research pharmacy.

The first day of the medication will be day 1 and subjects will be scheduled for a phone visit with the study team at day 7 and day 42 (or the next business day if this falls on a weekend). A check in call will be made by the study team 48 hours after starting the treatment to address any patient questions or concerns. For days 1-7, patients will take 30mg of duloxetine once a day, in the morning. Starting day 8, participants tolerating the medication will be escalated to 60mg once a day. They will also have the option of staying at 30mg, once a day or stopping the medication (see Figure 9 below).

Participants will be scheduled for a phone visit with the study team at the end of week 1 to discuss dose escalation and at the end of week 6 to discuss dose taper. At the end of the 8-week intervention period, participants will have the option to continue the medication commercially (non-study medication) under the care of their physician or taper off the medication. During the entire 8-week intervention, patients will be asked to keep a daily log of medication dosage, any missed doses, and any side-effects they may have experienced.

9.4.1 Dose Escalation

At the day 7 call, the study staff will document any adverse events and safety concerns the patients may have. Willing subjects will be asked to increase the dose to 60mg, once a day, in the mornings. Participants will also have the option of staying at a dose of 30mg per day or stopping the medication entirely. If day 7 is on a weekend, the call will be scheduled for the next business day.

9.4.2 Dose Taper

At the day 42 call, the study team will document any adverse events and safety concerns. Participants who are tolerating duloxetine and want to continue therapy using commercial medication, will be asked to obtain a prescription for duloxetine from their primary care physician, or other provider. The study team can provide a letter with drug information. If at this time the patient is not interested in continuing duloxetine, the taper schedule will be explained (see Figure 9 below).

- A patient at the max dosage of 60mg will be asked to tapered down starting day 56 to 30mg for 7 days and then 30mg every other day for another 7 days, before stopping the medication completely. These additional 11 pills will be provided to the patient at the post-intervention visit. If day 42 is on a weekend, the call will be scheduled for the next business day.
- A patient on 30mg, will be asked to start tapering on day 56 by taking 30mg every other day for another 7 days, before stopping the medication completely.

9.4.3 Duloxetine Post-Intervention Visit

When patients arrive for their post-intervention visit, the study team will document any adverse events, and/or safety concerns the participants may have. A daily log of medication dosage will also be collected from the patient at this point. Unused pills will be counted, documented and will be returned to the research pharmacy for accountability. Any additional pills for tapering will be provided for participants who want to taper.

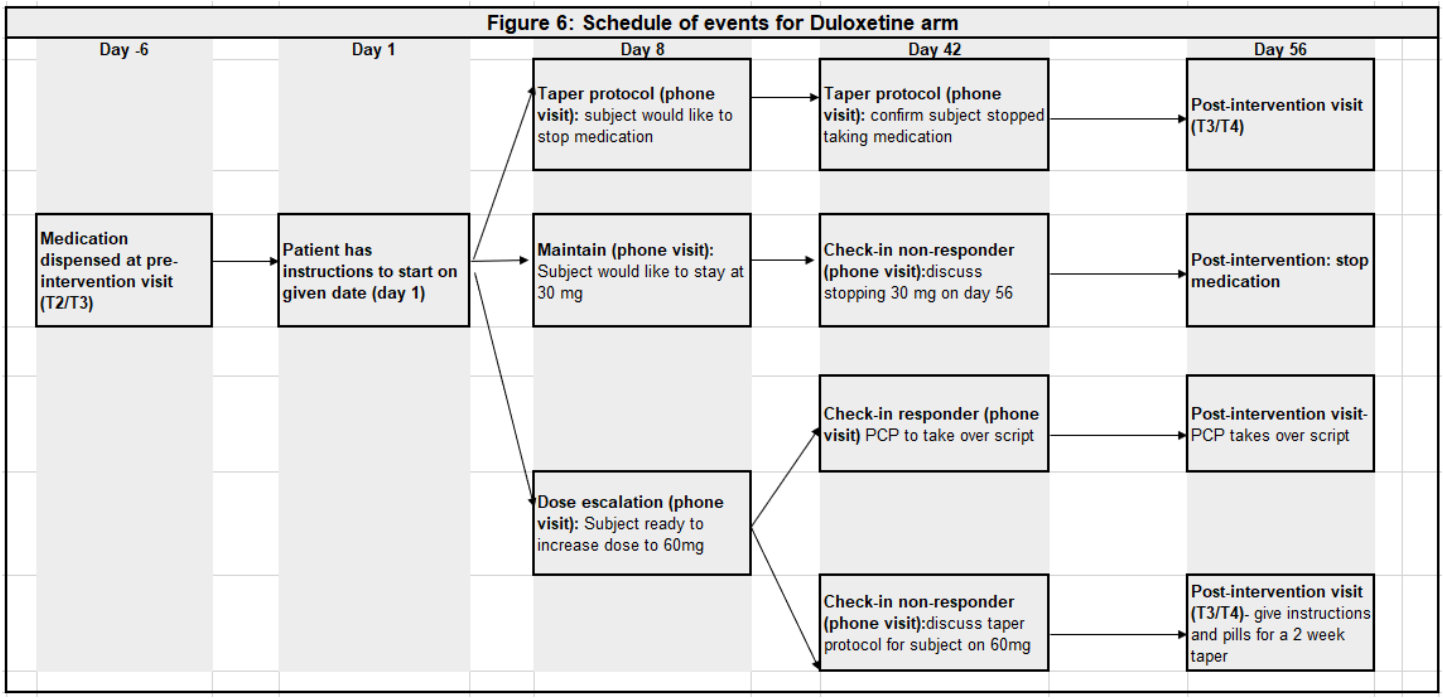


Figure 9 Schedule of Events for Duloxetine Arm

9.4.4 Medication Procurement and Storage

Medications will be procured from the research pharmacy on a weekly basis. Duloxetine will be stored in the research room's double locked cabinet. Temperature in the room must be managed between 20 -25ºc (68-77ºF); excursions permitted to 15-30ºC (59-86ºF) – per package insert. A log of maximum/minimum readings will be entered into a log while the drug is in research storage. Medications may also be mailed to patient directly, in the event of a lockdown due to COVID.

9.4.5 Medication Accountability

All study medication bottles will be collected/returned from the participant to the study team. When a bottle is returned, a study team member will count how many capsules or left and record the number on the bottle, date and initials. All medication bottles will be returned to the Research Pharmacy for drug accountability. The Research Pharmacy will be asked to sign off on the accountability log showing the bottle is returned. The Research Pharmacy will dispose of medication and bottles.

10 Deep Phenotyping Visits

A subset of study participants (n=160) be offered optional deep phenotyping. These participants will have a separate assessment appointment with study personnel at the CPFRC. There will be two visits that take place after T2-before Treatment 1 and after T3-before Treatment 2. At the deep phenotyping study visit, participants will undergo QST, Structural and functional brain neuroimaging, inflammatory markers assessment and the assessment autonomic functioning.

10.1 Quantitative Sensory Testing (QST)

Participants will complete a multimodal QST battery to characterize sensory function. Participant instructions are scripted, and all participants will undergo familiarization training for each procedure prior to data collection to reduce QST-related anxiety and measurement noise. All procedures can be stopped at any time by participant request if they become unbearable.

Pressure pain sensitivity will be assessed using an algometer with a 1-cm^2 rubber probe (FPK20, Wagner Instruments, Greenwich, CT, USA; or Algometer Type II, SBMedic, Solna, Sweden) to quantify pressure pain thresholds (PPT). The primary or "index" testing site will be located at the lower back by the participant's response to manual over-pressure (springing palpation). A control or "remote" site will be located over the contralateral trapezius or deltoid muscle (diagonal from lower back site). Multisite pain hypersensitivity, particularly at asymptomatic remote sites, is a core feature of centralized pain.[86,87] Pressure will be manually increased at a rate of 0.5 kgf/cm^2/s (10 kgf max, metronome guided as required) until participants first indicate that the sensation pressure becomes one of faint pain. Pressure intensity (in kgf) at that time will be recorded as the PPT. Measurements will be conducted 3x/site (separated by 20 – 60-s rest intervals) with means used for analysis. Probe placement will be varied slightly trial to trial to prevent tissue sensitization from repeated testing of the same site. Additionally, we will use the Multimodal Automated Sensory Testing (MAST) System (Arbor Medical Innovations, LLC, Ann Arbor, MI, USA) [88-91] to apply computer-controlled pressure at the thumbnail bed to derive a suprathreshold measure of pressure intensity that evokes a moderate level of pain (i.e., Pain50) as well as pain tolerance. We have extensive experience using thumbnail pressure as an evoked pain stimulus and its validity in the measurement of centralized pain has been demonstrated extensively.[92-104] The system delivers an ascending series of discrete pressures (5-s duration; 4 kgf/cm^2/s ramp rate) at 20-s intervals, beginning at 0.25 -.50 kgf/cm^2 and increasing in 0.25 - 0.50 kgf/cm^2 steps. Pain intensity will be rated after each stimulus on a 0-10 or 1-100 NRS. The test will be terminated when participants reach their tolerance or 10 kgf/cm^2. Lastly, large volume, deep muscle pressure sensitivity[105,106] will be assessed using a MRI-compatible rapid cuff inflator (Hokanson,Bellevue, WA, USA).[107-109] This system includes an air compressor, computerized pressure controller, and a 13.5 cm X 82.5 cm velcro-adjusted pressure cuff. Participants will first receive an ascending series of cuff pressures, starting at 20-60 mmHG and increasing in 10-20 mmHG steps (5-10-s pressures, 10-20-s rest intervals) to tolerance or to a maximum of 400 mmHG. Each pressure will be rated after deflation on a 0-10 or 0-100 NRS. These pain ratings will be used to interpolate a series of 8 tolerable cuff pressures that will delivered in pseudo-randomized order and rated individually on pain intensity and unpleasantness. Stimulus response curves will be constructed for each participant and used for analysis, along with several derived variables: *cuff-PPT, cuff-Pain50, and cuff-Tolerance*. In addition, tonic pain induced by continuous cuff pressure will be assessed (*tonic-Cuff)*. Each participant's individually calibrated Pain40-60 pressure (i.e., pressure that evokes a 40-60/100 pain rating) will be applied for 6-min to one gastrocnemius muscle. Pain intensity and unpleasantness ratings will be obtained every 60-s.

Conditioned pain modulation (CPM) procedures require a conditioning stimulus to induce endogenous analgesic systems and alter pain perception, and a test-stimulus to evaluate the endogenous analgesic response to the conditioning stimulus. CPM is attenuated in the majority of chronic pain participants and its magnitude is predictive of a variety of pain outcomes.[110-112] As in our previous studies, painful pressure delivered to one thumbnail by the MAST System will serve as the test stimulus; non-painful "touch" pressure (0.25 kgf/cm^2) or moderately painful pressure delivered to the contralateral thumb will serve as a neutral and a painful conditioning stimuli, respectively.[113-115] CPM magnitude will be calculated as the difference in pain ratings to the test stimulus applied prior to and during the conditioning stimuli, with reductions in test stimulus ratings during painful conditioning interpreted as evidence of intact endogenous pain inhibition. An alternative CPM procedure may be conducted instead using cold stimulation, consistent with the method of Locke[116] and others.[117,118] In this procedure, immersion of one hand into a circulating cold water bath (6-12°C; NESLAB Digital One RTE 7, Thermo Scientific, Newington, NH, USA or similar) will serve as the conditioning-stimulus and PPT at the lower back, trapezius or deltoid will serve as the test-stimulus. Baseline ratings of the test-stimulus will be acquired during the assessment of pressure pain sensitivity (see above). Conditioning stimulation will begin by immersing the hand to a level 10 cm above the wrist into the water bath. The hand will be immersed for 60 – 90-s (or to each participant's individual tolerance but not longer than 90-s); perceived pain of the water will be rated several times during hand immersion and at the time of hand withdrawal, using a 0-10 or 0-100 NRS, to determine the adequacy of conditioning pain.[119] After 30 – 60-s of hand immersion, lower back, trapezius or deltoid PPT will re-measured 2-3 times while the hand is still immersed in the cold

water or after it has been withdrawn. CPM magnitude will be calculated as the difference in mean PPT measured prior to and during the conditioning stimulus, with increases in PPT during conditioning interpreted as evidence of efficient endogenous pain inhibition.

Temporal Summation measures increases in excitatory pain pathways and is thought to reflect the progressive increase in dorsal horn neuronal firing in response to repetitive C-fiber stimulation.[120-123] Enhanced temporal summation is common in chronic pain and is predictive of pain outcomes.[124,125] We will evaluate temporal summation in triplicate using either a 256 mN pinprick (MRC Systems GmbH, Heidelberg, Germany), a 40 g Neuropen (Owen Mumford, Oxfordshire, United Kingdom), or a 300 g nylon monofilament applied to the lower back, as well as to the trapezius or the deltoid and/or the forearm, followed by a train of 10 identical stimuli (1 Hz). Following the single stimulus and the train of 10 stimuli, participants will report the pain intensity of the pinprick sensation using a 0-10 or 0-100 NRS. Temporal summation for each site will be calculated as the mean difference in pain ratings evoked by the single stimuli and the trains of stimuli. The degree of lingering pain evoked by this procedure, referred to as *pain aftersensations,* will also be recorded for up to 90-s following the last set of stimuli at each site.

Michigan Visual Aversion Stress Test (M-VAST) will probe mechanisms of sensory sensitivity that bypass somatic peripheral receptors and the spinal cord, and are amplified in many chronic pain participants.[92,126-128] Participants will be presented with a flashing annular checkerboard pattern at varying illumination levels as performed previously.[129] Participants will be acclimated to a dark room and exposed to a high resolution, calibrated LED monitor displaying the visual stimulus. Each visual stimulus intensity level and the entire task will be rated on both sensory intensity and unpleasantness scales. These rating will be used to compute stimulus-response curves for analysis.

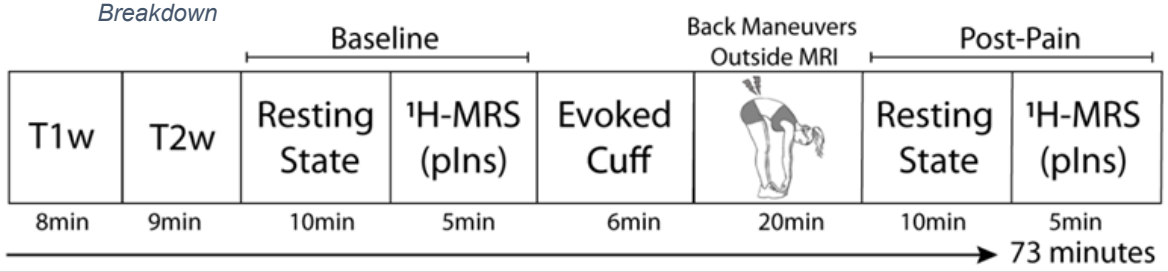
Two Point Discrimination Prior studies in participants with cLBP have documented subtle limitations in mechanical somatosensory sensitivity[130-132] and these are important to measure in a study of central nervous system processing of pain. Therefore, in addition to studying mechanical pain sensitivity, we will assess two-point discrimination thresholds, a measure of tactile acuity for non-painful mechanical sensation. As in previous studies, we will use a two-point aesthesiometer (BASELINE Evaluation Instruments, White Plains, NY, USA), applied to the lower back and to a (non-painful) control site on the upper limbs. Participants will complete series of ascending (in which the 2 points of the aesthesiometer are initially adjacent) and descending (in which the 2 points of the aesthesiometer are initially far apart) trials in which they indicate whether they “feel one or two points” when the stimulus is applied. The distance between the points is then either increased or decreased until the experimenter locates the minimum distance at which the participant perceives 2 points instead of one. The results of ascending and descending trials are averaged to calculate the two-point discrimination threshold. These procedures are commonly used in the practice of clinical neurology, are non-invasive and non-painful, and are not associated with any known risk.

QST Feasibility and Anticipated Results These procedures engage different aspects of pain perception and potentially different peripheral and central mechanisms, thus permitting a comprehensive investigation into the psychophysical characteristics of cLBP. This testing strategy has been extensively employed and validated by our group and multisite networks, including the NIDDK MAPP[90,133] and LURN[133,134] Networks, and the German Neuropathic Pain Network.[135] We anticipate no significant issues with implementation. As stated above, we hypothesize that cLBP participants with lower pain sensitivity at the thumbnail (i.e., higher pain thresholds) will respond to acupressure,[136,137] whereas those with diminished CPM will be more likely to respond to duloxetine.[138] We further hypothesize that participants with multiple indices of centralized pain, including generalized pain hypersensitivity (i.e., increased pressure pain sensitivity at the lower back and multiple remote body sites), facilitated temporal summation, and visual hypersensitivity, will preferentially respond to centrally-acting treatments. Lastly, participants with localized pain hypersensitivity at the lower back, but not at other body areas, will show preferential response to interventional procedures.

10.2 Magnetic Resonance Imaging

All participants will also undergo spinal MRI to assess structural abnormalities of lower back (see Section 6.6 for imaging on all participants). Additionally, a subset of participants enrolled in the deep phenotyping study will undergo four different brain neuroimaging procedures (Figure 10): 1) functional connectivity MRI (fcMRI) at rest, 2) proton magnetic resonance spectroscopy (^{1}H-MRS) of the posterior insula assessing combined glutamate and glutamine (Glx), 3) evoked pressure pain at a neutral site, and 4) voxel based morphometry to assess gray matter volume in S1 and primary motor (M1) cortex. Following physical maneuvers to exacerbate clinical pain, resting state fcMRI and ^{1}H-MRS scans will be repeated to assess the neurobiological response to increases in pain, as we have previously demonstrated in FM using pressure.[139] The methods described below have been successfully employed previously by our group, and probe different aspects of the brain's involvement in pain processing, thus complementing our QST methods by providing a comprehensive neurobiological signature of cLBP. Familiarization procedures will be completed prior to MRI to reduce anxiety. Neuroimaging will require approximately 90 minutes to complete. MRI will be done on a 3 Tesla scanner either at the Functional MRI Lab on UM North Campus (GE scanner) or in the Department of Radiology at the UM Main Hospital (Philips scanner).

Figure 10 Deep Phenotyping fMRI Breakdown



10.2.1 Resting State fcMRI

Brain imaging correlates of clinical pain have been notoriously difficult to measure;[140,141] however, our previous publications provide consistent evidence that our resting state fcMRI approach assays the neurocircuitry contributing to chronic pain as well as its modulation by pharmacological and non-pharmacologic interventions.[142-146] fcMRI is an adaptation of fMRI that examines intrinsic connectivity between brain regions - defined as ongoing synchronized neural activity occurring in the resting basal state. Intrinsic brain connectivity may be important for maintenance of synaptic connectivity and as such modulates the efficiency and extent of neuronal transmission between brain regions. Intrinsic connectivity, as measured by neuroimaging methods, follows known structural monosynaptic and polysynaptic pathways,[147,148] likely reflecting meaningful neurophysiological activity[149] within known primary sensory, executive, and associative networks.[150] fcMRI investigations are conducted with participants in an awake state, simply resting in the scanner. These data can then be analyzed with techniques such as independent component analysis (ICA), seed-voxel connectivity, and graph theoretical network techniques. While multiple resting state networks have been shown to be altered in chronic pain states, we will focus on two cardinal networks: the default mode network (DMN), and the salience network (SLN). The DMN[150,151] is a constellation of brain regions engaged in self-referential cognition, which are 'deactivated' during various externally focused tasks. Our group's data in FM have found increased connectivity between the DMN and insula, a brain region thought to integrate the multiple dimensions of pain.[152] Greater clinical pain is correlated with greater DMN-insula connectivity[145], which is also diminished following treatment.[143,144] The SLN, containing the insula, is largely activated when one's attention is focused on specific external or internal tasks.[153] This network is altered in centralized pain participants, primarily showing increased connectivity between the SLN and S1/M1.[154]

Data Acquisition. Our group has published extensively using resting state connectivity outcomes in both cross-sectional participant-control[144,155,156] and longitudinal treatment trials.[142-144] In brief, participants will undergo two resting state fcMRI scans; one will be at the beginning of the scanning session and the second will immediately follow the evoked low back pain maneuvers. Ten minutes of resting state fMRI data will be acquired using a T2*-weighted multiband echo planar imaging (EPI) sequence (TR/TE:720/33 ms, flip angle (FA) = 52°, matrix size 90x90 with 60 slices encompassing whole brain, field of view (FOV) = 180 mm x 208 mm, 2.0x2.0x2.0 mm voxels and 833 volumes, MB factor 8). During the resting state fMRI participants will be instructed not to focus on any particular task and stay awake with their eyes open and focused on a fixation cross. Since cardiac and respiratory fluctuations are known to influence brain connectivity,[157] these data will be collected simultaneously using a chest plethysmograph and infrared pulse oximeter. Only participant functional data of less than 2 mm of head motion inside the scanner will be included for analysis.

Preprocessing: fcMRI data are preprocessed using fMRIPrep (version 1.1.8)[158] running on the high-performance computing resources at our institution. Briefly, preprocessing steps include physiological noise removal (RETROICOR), motion correction, realignment, co-registration, normalization to standard MNI template, regression of nuisance variables (CompCor, motion parameters), and spatial smoothing (FWHM Gaussian kernel of 8mm).

Seed and Network (ICA) Connectivity Analysis. Seed to whole brain functional connectivity analysis is performed using the Conn (Cognitive and affective neuroscience laboratory, MIT, Cambridge, USA) functional connectivity toolbox. Seed regions (5 mm spheres) are chosen based on previously published fMRI studies of chronic pain, including: the insula,[146] and S1/M1.[154,159] Network seeds (DMN and SLN) will be derived from ICA, as previously published.[144,145,160] White matter, CSF, and motion parameters are used as covariates of no interest. Data is band pass filtered (0.01-0.1Hz) to remove linear drifts and high frequency noise from the data. First level analysis will correlate the time course from the seed/network to all brain voxels creating connectivity maps for each seed or network.

Group Level Analysis. Seed and network-to-whole-brain connectivity maps will be entered into a multiple regression model in SPM with change in pain interference (post minus pre-treatment) as a covariate of interest. Age and sex will be entered as covariates of no interest. Although not the primary objective of Aim 3, we will also conduct exploratory analyses to examine the mechanism of action of specific treatments. Changes in connectivity patterns following each of the phase 1 treatments will be performed using paired sample t-tests in SPM12. Resulting maps are thresholded at $p < .001$ uncorrected voxel threshold with $p \leq .05$ FDR significance corrected for multiple comparisons.

Graph Theory Analyses. Using Graph Theory Analyses the brain is defined as a network of 264 non-overlapping nodes (10 mm spheres) connected by edges or links.[161,162] These nodes and the preprocessed fcMRI data are entered into the Conn functional connectivity toolbox to create Fisher z-transformed bivariate correlation (Pearson's r) matrices (264 x 264) for each participant. To exclude weak or spurious connections, matrices are thresholded beginning with the strongest 5% connections and proceeding in steps of 5% up to 40% density, resulting in binary undirected graphs containing the most significant edges. Using the Brain Connectivity Toolbox,[163] we will calculate the following graph theoretical measures to assess global (efficiency, modularity, rich-club) and nodal (hub status) network properties, as previously published.[164] To assess hub status, we will calculate eigenvector centrality which takes into account the connectedness of a node, in addition to the connectedness of that node's neighbors. Hub status will be assigned to a node if the eigenvector centrality is greater than one standard deviation above the group mean.[165,166]

Group Level Analysis. We will determine if hub status and rich club organization predicts treatment response. Individual hub measures will be entered into regression analyses to predict ($p < .05$) association with change in pain interference pre- versus post-treatment.

Machine-learning based prediction analyses: SVM analyses will be performed for the previously mentioned modalities using the libsvm toolbox version 3.18[167] in Matlab 2017a and using group level images from the previously described modalities. Participant images will be labeled as a responder or non-responder based on change score of pain interference pre- versus post-treatment using a cutoff of a 30% reduction or a median split. SVM classification will be performed using a linear kernel with k-fold cross-validation to calculate classification accuracies. SVM model weights will be averaged across all cross-validation cases to investigate spatial distribution of the weights, with label permutation (n = X*1000) to establish significance levels.

10.2.2 Proton Magnetic Resonance Spectroscopy (1H-MRS)

During ^{1}H-MRS, quantifiable measures of brain metabolites will be acquired from multiple brain regions non-invasively. The metabolite we will focus on is glutamate, the brain's major excitatory neurotransmitter. Previous ^{1}H-MRS studies, performed by our group, have examined changes in Glx (combined glutamate and glutamine) in cross sectional participant-control[103,136,168,169] and longitudinal treatment studies.[104,143] We find that FM participants display elevated Glx within the posterior insula and this concentration is reduced following active treatment, and this reduction was correlated with a reduction in clinical pain.[143] We have also shown that pelvic pain participants have elevated Glx within the anterior insula which is in turn associated with increased connectivity to the medial prefrontal cortex, a DMN structure.[170]

Data Acquisition: ^{1}H-MRS will be performed as in our previously published studies.[103,143,170] In brief, we will examine Glx within the posterior insula twice (before and after back pain maneuvers). Our primary ^{1}H-MRS outcome will be baseline Glx within the posterior insula. ^{1}H-MRS studies are performed on the same magnet as fcMRI. PRESS (TR/TE=2000/35 ms) single voxel ^{1}H-MRS is performed on the region of interest with voxel sizes of 2x2x3 cm. The water signal is recorded using 8 averages. Standardized voxel placements are guided by visual inspection of anatomical T1-weighted images as reported previously.[103]

Preprocessing: Raw data from each single-voxel MR spectroscopy sequence will undergo manual post-processing using ^{1}H-MRS software (LCModel; Stephen Provencher, Oakville, Ontario, Canada). LCModel uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra.[171] Glx values will be calculated both as an absolute concentration using the water signal for normalization and as a ratio to creatine. Glx absolute concentrations will be reported in arbitrary institutional units. Correction for cerebral spinal fluid (CSF) volume, which can dilute ^{1}H-MRS-derived Glx values, will be performed as reported previously.[103] Metabolite concentrations will be excluded if the Cramér-Rao bounds are greater than 20%.

Group Level Analysis: CSF-corrected Glx values will be entered into a multiple regression model in SPSS with change in pain (post minus pre-treatment) as the dependent variable and Glx values as a covariate of interest. Age and sex will be entered as nuisance regressors.

10.2.3 fMRI of Evoked Cuff Gastrocnemius Pain

Whole brain blood oxygen level-dependent (BOLD) functional images will be acquired using the same 3 Tesla scanner and T2*-weighted EPI multiband sequence as described for the resting state scan. Each participant will undergo a 11-minute block design scan, during which 6 cuff pressures (equal pressure = 15-30 and 100-115 mmHg; equal pain = 40-60/100 numerical rating scale (NRS) units will be applied to the left calf using the pressure cuff device (described in Section 10.1) in pseudo-random order. Pain levels for each participant will be determined during the QST assessment. Each pressure stimulus will be applied for 14 seconds. Prior to each pressure stimulus, a 4-second visual cue will be presented to signal upcoming cuff pressure to limit any stimulus-onset startle reflex. Participants' head motion will be minimized using foam pads around the head, and a strap secured across the forehead.

Pre-processing: Same as resting state fcMRI. See Section 10.2.1.

Group level analysis: The activation maps (pain minus rest) will be entered into a GLM to determine the neurobiological correlates of evoked pain that best predict treatment response (change in pain as the dependent variable). In addition, SVM will be implemented to create a machine learning model for prediction and discrimination between responder and non-responder (see corresponding Section 10.2.1). Resulting maps are thresholded at $p < .001$ uncorrected voxel threshold with $p \leq .05$ FDR significance corrected for multiple comparisons.

Physical Maneuvers to Evoke Back Pain. During their initial in-clinic visit, participants will perform simple exercise-like maneuvers (e.g., arching/bending the back to elicit lumbar flexion/extension) to evoke temporary increases in back pain. The experimenter will measure the degree to which a participant must flex or extend their back to evoke a clinical pain increase of at least 30% over their baseline. Detailed records will be taken of frequency and duration required to achieve the targeted clinical pain level to ensure the same maneuvers are performed at subsequent fMRI visits. For each participant, individualized physical maneuvers that are most reliable in exacerbating clinical pain will be picked for the fMRI sessions. During fMRI, participants will undergo baseline functional imaging (capturing brain activity at their baseline pain level), followed by a short (15-20 minute) break whereby participants will perform the physical maneuvers outside the scanner. Participants will re-enter the MRI environment and undergo post-exacerbation functional imaging (at their elevated pain level). Imaging analyses will focus on changes in brain activity within an individual (from baseline to exacerbated back pain). Participants will be cautioned to not increase their pain to a level that they are unable to tolerate. This procedure to exacerbate clinical back pain levels has been well-tolerated, feasible, and extensively used in past research,[172-174] however participants that are uncomfortable or concerned about performing this task can choose to skip it and complete the remainder of the fMRI session.

Autonomic Nervous System (ANS) acquisition during fMRI. During each fMRI scan, electrocardiogram (ECG), photoplethysmogram (PPG), respiration, skin temperature, and GSR data will be collected at 500 Hz using an MRI-compatible, noninvasive BIOPAC MP160 System (BIOPAC Systems, Goleta, CA, USA). For the ANS outcomes, ECG and respiratory volume signals will be acquired with 2 MR-compatible Ag/Ag-Cl transcutaneous sensors placed above and below the heart and a pneumatic belt placed just below the rib cage. GSR, PPG and temperature will be acquired using MR-compatible Ag/Ag-Cl transcutaneous sensors placed on the fingertips of the index and middle fingers.

Analysis: Inter-beat-intervals (segmented into 5-minute windows) and GSR signals (15-second epochs) will be imported into MATLAB for feature extraction. Windows with >15% missing data will be excluded. HRV features, including all time- and frequency-domain and Kubios features,[175] and tonic and phasic GSR features,[176] will be extracted using MATLAB. After feature extraction, we will utilize a semi-supervised machine learning paradigm[177] to combine the continuous HRV and GSR signals and characterize vagal tone.

Feasibility. We have previously collected ANS activity in participants undergoing QST and neuroimaging without difficulty. Risks associated with these measures are minimal since they are non-invasive. However, some participants may experience anxiety and/or a general unease associated with unfamiliar physiological testing and/or when applying or removing sensors. Participants will be instructed that they may stop participating at any time.

10.2.4 Brain structural Imaging with Voxel Based Morphometry (VBM)

We have published extensively using VBM methods in various chronic pain states.[178-181] In brief, our protocol includes T1-weighted structural images (TR 2400/TE 2.14ms; Flip angle 8 deg; FOV 224X224; Voxel size 0.8mm isotropic) segmented into white matter (WM), gray matter (GM), and cerebral spinal fluid using the

segment function in SPM12, running under MATLAB 2017a. The resulting GM segments are then processed using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) toolbox.[182] We will normalize VBM data are to standard space. We will smooth normalized, modulated images with a Gaussian kernel, and pass individual participant maps up to group level analysis.

Group Level Analyses: We will enter smoothed GM images into a multiple regression model in SPM12 with change in pain interference (post minus pre-treatment) as the covariate of interest. Age and total brain volume will be entered as nuisance regressors. We will exclude voxels with GM values < .1 from analysis.

Feasibility: We anticipate few problems in data analysis based on our past studies.[154,178-181]

Feasibility and Anticipated Neuroimaging Results. We have published extensively in the field of fcMRI, evoked pain fMRI, and ^{1}H-MRS, and expect no issues with data acquisition or analyses.[102-104,115,129,136,142-144,146,155,156,168,183-186]

10.3 Biospecimen Collection for Inflammation Methods

No more than 10mL of blood will be collected at each deep phenotyping visit. All samples will be stored initially at the University of Michigan but may be sent to other MRCs or central biorepositories for future storage or additional analyses.

Stimulated Assays. The TruCulture system (Myriad RBM) consists of small vacutainers preloaded with immune stimulants (e.g., LPS) or control media into which whole blood is drawn. Following incubation in a small table-top unit, the supernatant is isolated without the need for centrifugation using a small plunger included in the kit. Whole blood is drawn via venipuncture into two different 1 mL tubes containing lipopolysaccharide (LPS; 100 ng/mL), or media (NULL). LPS is potent agonist of TLR4,[187] Samples are immediately incubated at 37° C for 24 hours, after which the supernatant is isolated with a valve separator included in the kit. The supernatant is frozen at -80° C prior to shipment to a biorepository where it is thawed, aliquoted into 0.25 mL containers, and stored at -80° C for batch analysis. All batches include control standards (i.e., samples provided by lab personnel) to allow for estimation of batch effects.

Cytokine/Chemokines are analyzed from supernatant using multiplex Luminex xMap technology or equivalent. We have completed a series of dilution protocols to determine optimal concentrations to keep each analyte in the dynamic range of the assays. A minimum of seven cytokines/chemokines will be analyzed from each sample including those in the pro-inflammatory NF-κB- mediated suite (IL-1β, IL-6, TNF-α), chemotactic cytokines (IL-8, MCP-1, MIP1α), and regulatory cytokine IL-10.

Analyses: Cytokine/chemokine data often does not follow a normal distribution, which can create issues when using parametric statistical approaches. Therefore, we will evaluate normality with the Shapiro-Wilk test statistic and apply Box-Cox transformations where required. Any values below the lower limit of detection will be set to half that value. Multi-level models will be employed that can accommodate random effects for each batch analysis (in case significant variation is observed between-batches), and for site of collection.

Feasibility and Anticipated Results. The protocol developed for MAPP serves as a template for this proposal because we have demonstrated that the procedures can be implemented with minimal training and without the need for dedicated wet lab space at the site of collection. In the second phase of MAPP, more than 95% of participant visits have resulted in analyzable samples across all three conditions. The stimulated assays are also clearly effective: in 198 samples from a preliminary MAPP II analysis, LPS-stimulated IL-6 showed a median increase of 21,000 pg/mL compared to media (unstimulated condition) while LPS-stimulated MIP1a showed a median increase of 48,000 pg/mL over media. We have also conducted a small analysis of freeze/thaw cycles as two such cycles are currently required for this protocol. After eight cycles, there was no evidence of change in analyte (e.g., IL-6, IL-1) levels.

Gene expression. Approximately 2.5mL of whole blood is drawn into the PaxGene® blood RNA collection tubes containing approximately 6.9mL of proprietary stabilizing reagent. The tube is gently inverted 8-10 times and allowed to stand at room temperature for 2 hours at which point the same tube is frozen at -30-80° C for batch analysis.

Analyses. Differential gene expression will be assessed using standard linear statistical models including effects of any covariates such as age and gender. We will identify all gene transcripts based on thresholding of >1.15-fold differential expression between treatment responders and non-responders.

Sex hormones. We may also collect 5 mL or less of blood into "red top" containers and allowed to clot for 15-30 minutes. Samples are then centrifuged for 10-20 minutes at 1000-2000 rcf for isolate of serum. These are subsequently aliquoted into .5-2 mL cryovials and stored at -80^0 C for batch analysis of hormones (e.g., testosterone, GnRH, LH and FSH).

10.4 Unscheduled Non-Study Interventions Triggering Deep Assessments

It is anticipated that 10-20% of enrolled participants will get a non-study related invasive or minimally-invasive pain intervention including back surgery, epidural steroid injections or facet joint injections while enrolled in the study. To assess these common pain medicine interventions that take place outside of the study, monthly assessments will ask about plans for new treatments and also request that participants contact study staff if one if these treatments is scheduled. Participants who meet the deep phenotyping inclusion criteria will be offered an additional deep assessment visit ***prior to*** the medically scheduled pain intervention. Should the participant agree, then a deep phenotyping visit will be scheduled at the CPFRC to take place in advance of the intervention. Data will also be collected exploring why the patient chose to undergo this non-study intervention (e.g., not satisfied with current treatments, physician prescribed new treatment). Then, at 4 and 8 weeks after the non-study intervention participants will undergo a separate follow-up assessment (same as that used for the BACPAC consortium non-study intervention surveillance, see Section 11 below).

11 Other Unscheduled, Non-Study Interventions (NSI) Follow-Up Assessments

Other non-study interventions (NSI) are expected to occur during the course of a patient's enrollment and will be assessed once per month for the first 6 months of study enrollment during T1-T4 and during mini-assessments as appropriate. An affirmative response regarding starting one of these NSI will trigger a short follow-up questionnaire assessment consisting of a Patient Global Assessment of Change (PGIC), pain intensity as measured by PROMIS Pain Intensity and the Low-Back Pain Specific Pain Intensity, and the PROMIS Pain Interference (4a) delivered via Qualtrics at 4 weeks and 8 weeks after the treatment. We will also assess the reasons for starting the new treatment. These follow-up assessments will only be triggered for the first NSI scheduled for a participant. Later NSIs will only be logged and inform data analysis. Treatments that will trigger these follow-up assessments are listed below:

1. Spinal fusion
2. Injections for low back pain
3. Changes to medication for low back pain
4. Spinal adjustment/manipulation, physical therapy or occupational therapy supervised by a chiropractor, physical therapist or occupational therapist, or direct non-medication treatment such as ultrasound or diathermy for low-back pain
5. New exercise routine to manage back pain
6. Acupuncture
7. Mental health therapy or counseling
8. Mindfulness, meditation or relaxation
9. New diet or weight loss program
10. Any other new non-study treatment for low back pain

12 Study Measures and Questionnaires

Validated questionnaires will be used to assess many of the variables of interest. The measures and their assessment time points are depicted in Section 1.3. Questionnaires will be completed by participants at all visits T1-T5 and there will be additional mini-assessments described below. Additionally, study surveys will be completed by participants in the MBSR and physical therapy interventions (see sections 9.1 and 9.2).

12.1 Mini-Assessments

Participants will also be asked to complete electronic questionnaires every 2 weeks throughout the study. There are a total of 17 mini-assessments and those in weeks 1, 6, 15, 24 and 36 will be completed as part of the study visit survey (T1-T5). There will be 12 additional mini-assessments will take place at weeks 3, 8, 10, 12, 17, 19, 21, 26, 28, 30, 32 and 34. There are three types of mini-assessments- standard, expanded and mediation and these are described below.

12.1.1 Standard Mini-Assessments

There are 10 standard mini-assessments and they are done at assessments done at weeks 3, 8, 10, 17, 21, 26, 28, 30, 32, and 34. These will be sent electronically to participants through Qualtrics.

12.1.2 Expanded Mini-Assessment

There will be an expanded version of the mini-assessment that takes place close to 3 months (week 12 after baseline). The expanded version at week 12 will include added measures to comply with BACPAC minimum dataset requirements.

12.1.3 Mediation Mini-Assessment

There will be a mediation mini-assessment at week 19. This will have the same surveys as the standard and expanded mini-assessments. Additionally, there will be 3 surveys not in the other assessments. These are described in Section 1.3.

13 Subject Incentives

Table 4 Breakdown of Participant Incentives for Study Activities

Subjects will receive incentive payments upon completion of each study visit and will be eligible for a total payment of up to $1370. Participants can receive up to $600 for the light phenotyping, up to $500 for the deep phenotyping, up to $260 for an unscheduled deep phenotyping visit and $10 for an unscheduled non-study intervention follow-up assessment (see Table 4 Breakdown of Participant Incentives for Study Activities).

13.1 Light Phenotyping Incentives

All participants will be eligible for a total of $550 for completing the light phenotyping portion of the study. They will receive $40 upon completing each of the five study visits. For the first visit, subjects will be paid an additional $10 if they complete blood draw, $90 for MRI and $5 for parking at the MRI site. Subjects will be paid $50 for completing the physical exam and vitals. Subjects will be paid $15 payment upon completion of the five EMA assessments. Subjects will be paid $10 for each of the 12 mini-assessments. Subjects randomized at the T2 study visit will receive $50 for completing 80% of the treatment. Those who do not meet this threshold will not be compensated. Participants will receive a non-monetary incentive (study logo water bottle and backpack) at the T2 and T3 visit.

13.2 Deep Phenotyping Incentives

A subset of 160 subjects will undergo deep phenotyping with two additional study visits and will be eligible for $245 for each of the two visits ($500 total). For each of the first and second deep phenotyping assessment including QST, subjects will be compensated $100, an additional $145 if they complete the fMRI and blood draw and $5 for parking.

13.3 Unscheduled Deep Phenotyping Incentive

Subjects that have unscheduled deep phenotyping visits will be offered one additional visit and be eligible for $260. For the unscheduled deep phenotyping assessments including QST, subjects will be sent $100, an additional $145 if they complete fMRI and blood draw, and $5 for parking. Subject will be sent $5 upon completion of the 4 weeks post PGIC assessment and 8 weeks post PGIC assessment, respectively.

Study Activity	Payments
All Participants	**$600**
Study visits (5 total)	$40 ($200)
Blood draw	$10
Vitals and physical exam	$50
MRI	$90
Hospital parking	$5
Symptom monitoring (EMA-5 total)	$15 ($75)
Mini-assessments (12 total)	$10 ($120)
Completion of 1st treatment	$50
Optional Deep Visits	**$500**
Study visits (2 total)	$100 ($200)
fMRI and blood draw (2 total)	$145 ($290)
Hospital parking (2 total)	$5 ($10)
Unscheduled Deep Visit Triggered by Non-Study Intervention	**$260**
Study visit	$100
fMRI and blood draw	$145
Follow-up surveys (2 total)	$5 ($10)
Hospital parking	$5
Unscheduled Non-Study Intervention Follow-up	$**10**
Follow-up surveys (2 total)	$5 ($10)

13.4 Unscheduled Non-Study Treatment Incentive

For other unscheduled, non-study treatments triggering 4 and 8-week follow-up assessments, participants will be eligible for $5 for each of the two assessments completed ($10 total).

13.5 Lodging

Patients traveling from more than 60 miles may be offered lodging for their study visits.

14 Post-Intervention Assessments (T2-T5)

Participants will be scheduled for a return visit immediately before and after each intervention period (T2, T3, and T4) and at 3 months after the final scheduled treatment period (T5). These visits can occur virtually or as a hybrid visit combining online and in in-person data collection. At the follow-up, changes in medications will be elicited and cross-referenced to the EMR, with an emphasis on use of opioids, new diagnoses, and other interventions. The effect of adherence on outcome will be explored. Data maybe

collected in one of two ways; by either an in person at the Back & Pain Center or done remotely through a virtual platform. There is also a series of 12 brief online mini-assessments interspersed within the light and deep phenotyping visits, such that participants will have key PROs collected every 2 weeks for the study period (see Section 12.1 for mini-assessments and section 1.3 for specific questionnaires being collected at each time point).

15 Retention

In regard to retention, the study team's priority is to facilitate and support subject participation in the study (i.e., lessen patient burden). When possible, research appointments will be scheduled on the same day as standard of care appointments. Research appointments handled through the Back & Pain Center are scheduled through the electronic medical record system, MiChart, and thus appointment reminders are automatically sent via text and an automated call system prior to the appointment. This strategy alone has done much to assure patient attendance at clinical research assessment appointments. Additional reminders will be sent via email, text and phone calls. Most data collection visits will use a hybrid approach where questionnaire data will be collected online, while clinical data such as vitals, biospecimen collection and functional testing will occur at the Back & Pain Center. This strategy greatly decreases the time required on site and also breaks up the study visit, thus decreasing participant burden.

Furthermore, interventional arms like acupressure will use the push notification functions to engage patients throughout the intervention, while other interventions utilize various engagement strategies such as engaging eHealth "homework as occurs in MBSR. Throughout the study, participants will have one point of contact through the Back & Pain Center (light phenotyping) or the CPFRC (deep phenotyping) to provide consistent communication and support. Participants will receive general study updates that emphasize the participant's contribution to clinical pain research. Lastly, participants will receive thank you card for their time and effort in this study. All of these elements can help promote retention and engagement for the proposed study period.

For purposes of the integrity of the study, participants who miss a study visit, study staff will follow up with them three times to reschedule that visit. If the participant is unable to be reached, it will be reported electronically in the database as missed. Attempts will be made again to follow up at the next study visit window. If there is no contact with the patient for 9 months, it will be reported as the participant was lost to follow up.

16 Data Management

All data collected on study participants will be obtained and managed specifically for research purposes. The types of data to be collected in aggregate across projects include medical status and history; self-report questionnaires that assess physical and psychological symptoms and life functioning, physical exams, functional performance measures, participant responses to all QST and physiological performance measures; biospecimens and neuroimaging data (^{1}H-MRS, fMRI, functional connectivity MRI).

All assessment forms will be collected either via a web-enabled Electronic Data Capture System (EDC) or on paper then entered into the study database by a member of the research team at a later date. The EDC website will be available via secure access and security will be implemented using firewalls, unique user IDs and passwords, secure socket level (SSL) encryption, trusted third party certificates, and standard operating system maintenance, backups and patches. All completed paper forms containing data will be kept in a secure, locked filing cabinet located at the University of Michigan's Back & Pain Center or the Chronic Pain and Fatigue Research Center (CPFRC) in Ann Arbor, MI, USA.

The Michigan EDC system for this study will be a protected, industry-leading survey system such as Qualtrics Redcap, or Choir, which follow all regulatory requirements regarding participant confidentiality and human participant safety and backs up all data every 24 hours. A study team member will serve as the database manager. Where Qualtrics is not used, SPSS Data Entry software will be used for initial data management quality control because it has the built-in functions to automatically compare for potential errors and logic discrepancies. Downloaded data files will be stripped of PHI, password protected and stored on the secure S

drive, a HIPAA-compliant network drives used by the Anesthesiology Department at Michigan Medicine and managed by the Anesthesiology Department's Informatics division.

Imaging data will be obtained using one of two 3.0 T GE MRI scanners located at the Functional Magnetic Resonance Imaging lab at University of Michigan or at the University Hospital 3.0 T Philips scanner. The two GE scanners are completely dedicated for research and have identical operating systems and pulse sequences allowing for flexibility in scheduling. Imaging data will be de-identified and stored on secure, password-protected HITS servers. All analyses will be performed at the CPFRC.

Participants will also be asked to provide blood samples. All blood samples will be de-identified prior to storage. All samples will be collected, securely stored, and processed for disbursement and analysis by appropriate study investigators. Participant identity and confidentiality will be maintained throughout.

17 Data, Sample Storage and Sharing

Study data, biospecimens and neurobiological data will be stored securely at the Back & Pain Center or the CPFRC in Domino Farms at the University of Michigan or at sites NIH selects for this study. Data and samples will be stored indefinitely. Participant names and other personally-identifying information will not be kept with the data or samples. Data and samples will either be stored without a code linking them to the subject or they will have a code that links to identifying information. If data has a code, the key to the code will be kept at Back & Pain Center, the CPFRC at the University of Michigan or electronically to be used for patient tracking. This code will be kept in a separate, secure area and will not be shared outside of University of Michigan.

Accelerometer/EMA data from the PRO-Diary, AcuWand data and MBSR recordings all will be stored and shared internally via Dropbox, which is Michigan's HIPAA compliant cloud storage and collaboration service. It is capable of handling PHI and other sensitive data (e.g., research data). After it is cleaned and scored, the PRO-Diary data will be later merged with the REDCap data prior to analysis.

17.1 Data Sharing

This study is part of the NIH HEAL Initiative focused on understanding and developing new treatments for addiction and pain. Data and samples will be used for this and other NIH HEAL Initiative studies. Stored data and samples will also be made widely available to other researchers. The shared data and samples may be used indefinitely for research not related to this study or the HEAL Initiative, without asking for additional consent. Samples collected for this study contain DNA. Genetic information may also be used for research unrelated to this study. Participants can withdraw from this research study before it is done. Samples and data that have already been collected will be kept and used for analysis.

Data collected for this study will be cleaned and stored at the University of Michigan. A limited data set will be shared with the University of North Carolina (UNC) which acts as the Data Coordinating Center for the BACPAC Consortium (a HEAL Initiative).

17.1.1 Frequency of Data Transfers to the UNC DAC

The initial "test" transfer of data will be performed when approximately 10% of participants have been randomizedand at least some participants have completed for each research project. Cumulative data transfers will be performed after 20%, 40%, …, 100% of participants have completed a study AND when their data are viewed as stable (e.g., no outstanding data quality issues as defined in the study's data management plan).

17.1.2 NIH Data Sharing Policy

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

In addition, this study will comply with 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. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

17.1.3 Data Sharing Outside of the BACPAC Consortium

Data from the UNC DAC may be shared with investigators outside of the BACPAC Consortium. These requests will be reviewed for approval by the Data Access and Publications Committee (DAPC). The DAPC is made up of one representative from each of the BACPAC funded units: Mechanistic Research Centers, Technology Research Sites, Phase 2 Clinical Trial sites, and the DAC, and an NIH representative.

17.1.4 Data Banking, Sharing, Storage, and Retention for the Pheno Device

Data collected in this study, including sex, birth year, height, weight, motion assessment data, information from the participant's medical record related to their spine condition (such as demographics, symptoms and diagnoses), and answers to questionnaires will be stored electronically in a digital cloud platform managed by Ohio State University. The Ohio State Pheno platform is powered by an Amazon Web Services (AWS) server that is equipped to handle data securely. Data will be stored on secure and encrypted servers residing within the United States. Only Michigan and OSU researchers or personnel authorized by OSU administration will have access to the cloud platform and the data shared with OSU. Note that participant data may be shared with individuals outside of OSU or the Department of Defense. Data will be stored indefinitely.

There is a slight risk of breach of confidentiality or that someone might gain access to participant data that is not authorized to do so. To protect against this risk, OSU will not be receiving data with Personally Identifiable Information (PII) such as birthdate, name, or contact information, will ensure that data is encrypted, and has gone through a thorough Security Risk Assessment at OSU to be able to store protected health information (PHI).

If a participant agrees to participate in the study, their data will be considered a gift to The Ohio State University. The university may sell or share participant data with others, such as private companies, government agencies, or other universities. The university will be paid if participant data are sold. Participant data may be used to make new products or technologies. Participants will not be paid if these new products or technologies are sold or make money. Participants cannot choose how their data will be used. If participants do not want to let others decide how their data will be used, they should not donate their data or participate in the study.

If participants would no longer like their data to be included in the data repository, they withdraw from the study by contacting the study team to end their participation. Their data will no longer be used for future efforts and will be removed from the data repository. Due to the permanent nature of publishing data or reporting data for commercialization efforts, OSU cannot remove data that was previously used.

Note that data from this study will be combined with other similar databases at OSU in a data repository or data bank to support other related or unrelated research, development, and commercial purposes without additional consent from enrolled subjects. In particular, researchers will compare data collected here with similar databases of control, low back pain, and neck pain subjects to understand similarities and differences between these cohorts.

18 Statistical Design and Analysis

The analyses will be led by Dr. Tsodikov, blind to group assignment. We will focus on predicting differential analgesic responses to treatments and other secondary endpoints (multi-dimensional symptoms, functional outcomes, pain beliefs and coping) based on the longitudinally measured patient phenotypes. The objectives of the mechanistic analysis include development of a tool for prediction of the treatment response based on a multi-dimensional feature panel measured at baseline (a study of treatment effect moderators), as well as gain some exploratory structural insights into the causal relationships between light and deep phenotyping

measures (mediation analysis), thus implicating some of the factors as being part of a causal pathway to a specific treatment benefit. Another key objective of the analytic approach will be to build a toolbox of analytic methods and algorithms of data processing to be able to support unanticipated needs of the Research Project and other Cores with custom method compilation and new methodology development to support emerging hypotheses testing in the course of the project and its collaboration with other MRCs. In the sections below we outline our main analytic approach, as well as the power considerations for testing key hypotheses. See Section 1.3 for summary of when various data points are collected.

18.1 Exploratory Mechanistic Analysis

The following mechanistic analyses will explore a wide range of variables that may predict treatment response.

18.1.1 Mindfulness-based Stress reduction (MBSR)

Predictors of response in light phenotyping (Aim 2). We have *a priori* hypotheses regarding the PROs that will identify a subset of cLBP patients who will preferentially respond to a pain-related MBI, in particular, in psychological / emotional components of reactivity to pain that can exacerbate pain unpleasantness and interference. Since MBIs have shown efficacy for both centralized/nociplastic and neuropathic pain as well as nociceptive pain, we predict MBIs will show similar efficacy across these pain types. We predict that cLBP patients will preferentially respond to this therapy if PROs indicate *higher levels of pain catastrophizing,* as measured by the PCS, or *lower scores on the Experiences Questionnaire.*

Predictors of response in deep phenotyping (Aim 3). After a 4-week MBSR course, chronic back pain patients had significantly increased activity in the subgenual ACC (sgACC) and ventrolateral PFC – two regions known to play a critical role in the descending inhibition of pain.[92] These results are supported by a study of healthy volunteers conducted by Zeidan et al.[46] that found increased activity in the sgACC, as well as orbitofrontal cortex and insula and decreased activity in the S1 and thalamus during evoked pain stimulation following mindfulness training. These studies suggest MBSR acts in part by enhancing central inhibitory responses to pain. We therefore hypothesize that cLBP patients with *decreased activation in response to pain in the sgACC and PFC* and *increased activation in S1 and thalamus* will respond preferentially to MBSR.

18.1.2 PT/exercise

Predictors of response in light phenotyping (Aim 2). Most of the studies to date that have attempted to identify factors most predictive of differential responsiveness to exercise in cLBP have been based on some variation of the cognitive behavioral fear avoidance model, wherein low functional self-efficacy for exercise is related to high pain catastrophizing and fear of movement.[93-97] This cognition has been shown to promote the transition from acute to chronic low back pain, as well as to be associated with worse chronic low back pain.[97-99] Our primary hypothesis for the light phenotyping protocol is those individuals with the *highest scores on the Fear Avoidance Beliefs Questionnaire (FABQ)* and *lowest scores for PROMIS Self-Efficacy for Managing Symptoms* will be most likely to improve from our PT program, which is focused on getting participants over this fear of movement.

Predictors of response in deep phenotyping (Aim 3). Studies using QST or functional neuroimaging have suggested that aerobic exercise may lead to pain improvement in part via augmentation of descending analgesic pathways.[100-103] This is also supported by the fact that humans and animals who are actively exercising are less pain sensitive (mainly to mechanical stimuli) than controls.[104-107] Both opioidergic and non-opioidergic (e.g. norepinephrine) pathways are believed to exert these effects. Furthermore, elevated basal inflammation (e.g., CRP, IL-6) is associated with both the presence and severity of cLBP even after adjustment for potential confounding variables like obesity.[108,109] However, the exercise programs used in cLBP (and proposed in our MRC) are rarely aiming to get patients to do aerobic exercise. Instead, these programs initially focus on stretching and strengthening, as well as encouraging more activity and movement. We feel that the E4 device we propose to use in deep phenotyping will give us two measures that will predict responsiveness to our PT/exercise program: *low baseline activity levels* as measured by the actigraph, as has been previously shown,[96,110] as well as *low parasympathetic tone* as measured by the heart rate variability high frequency (HF)

power measure from this device.[111] We have extensive previous experience using HRV measures to infer autonomic tone, and this measure has been shown in several studies to improve following the milder exercise programs such as the one we propose.[112-120] There are also many other lines of research that show that vagal tone is low in many chronic pain patients and related to the duration of time individuals have had chronic pain.[121] Many treatments including exercise may exert some of their associated analgesic effects by augmenting vagal tone.[122-127] Exercise is known to exert anti-inflammatory effects and has been shown to decrease levels of inflammation substantially.[128,129] We therefore anticipate that *low vagal tone* and *high basal inflammation* will predict responsiveness to the PT/exercise program.

18.1.3 Acupressure.

The possible underlying mechanisms explaining how acupressure improves pain are currently unclear. A review by Zhao[130] suggested that some effects of acupuncture, a related technique that stimulates the same body sites with needles instead of pressure, are mediated by a number of brain neurotransmitters including norepinephrine, melatonin, gamma-aminobutyric acid (GABA), and β-endorphin which are relevant for pain and co-occurring sleep dysfunction. Acupuncture studies using functional and structural MRI have shown needling to reduce sensory cortex and limbic system excitability,[131,132] regions which are intimately involved in pain. Our own fMRI study, which examined the effects of two acupressure formulas --relaxing and stimulating -- in breast cancer survivors, found that different types of acupressure work via different mechanisms within the brain.[133] Relaxing acupressure increased connectivity between the superior colliculus, a brainstem region important in regulating sleep, and Default Mode Network (DMN). These data suggest a central nervous system action of both acupressure and acupuncture.

<u>*Prediction of response in light phenotyping (Aim 2).*</u> The literature regarding prediction of acupressure effects is minimal. However, as mentioned above, these therapies are thought to work primarily via central nervous system mechanisms. As such, we feel that they should be more effective in centralized/nociplastic pain. Although no groups that we are aware of have looked directly at this issue, our group has preliminary unpublished data in cLBP patients treated with acupuncture (n = 19; treated 6 times over a 4-week period with pain assessed prior to and immediately after each treatment, and widespread pain assessed by the number of body regions having pain) showing a significant relationship between increased baseline widespread pain and subsequent acupuncture response (Standardized Beta [adjusting for age and sex] = 0.58, t = 2.1, p = 0.048). These pilot data suggest that centralization of clinical pain may be an important marker of acupuncture treatment outcome. In further support of this hypothesis Witt et. al. noted that females were more likely to respond to acupuncture than males, a phenomenon that is noted when treatments work primarily in the CNS, as with duloxetine.[134,135] As such, we predict that *females* with cLBP will respond better to acupressure than men, as will those with *higher scores on the 2011 Fibromyalgia Survey Questionnaire (FSQ)*.

<u>*Prediction of response in deep phenotyping (Aim 3).*</u> We are aware of no studies to date that have examined the predictive ability of QST or our other deep phenotyping methods in determining pain improvement following self-administered acupressure. That said, in the context of acupuncture, we were one of the first to show that pressure pain thresholds at baseline were differentially predictive of verum (active) and sham acupuncture.[136,137] Patients who had higher pain thresholds were more likely to respond to verum acupuncture. There seems to be an uncovered relationship between sensory cortex brain activity and acupuncture response, as the primary somatosensory cortex (S1) has been shown to be involved in acupuncture effects in other pain conditions.[132] We predict that cLBP patients with *higher pain thresholds* on QST will respond better to acupressure. In agreement with the sensory system playing a role in acupuncture treatment, we also found a significant correlation between the reduction in posterior insula glutamate and chronic pain in centralized pain patients following acupuncture.[138] We also found similar relationships between insula to DMN connectivity wherein reductions in this connectivity were correlated with improvements in clinical pain following acupuncture in this population.[139] As such, we predict that cLBP patients with *higher posterior insula glutamate* and/or *greater insula – DMN connectivity* (as well as *increased DMN-SI connectivity* – please see NPC preliminary data) will display an improved analgesic response to self-acupressure.

18.1.4 Duloxetine

Predictors of response in light phenotyping (Aim 2). We have several *a priori* hypotheses regarding the PROs that will identify a subset of cLBP patients who will preferentially respond to duloxetine, or another similar SNRI. We hypothesize that we will replicate previous studies suggesting that cLBP participants will preferentially respond to this therapy if PROs indicate s*tronger elements of either neuropathic pain (indicated by a high PainDETECT score*[140,141]*)* or *centralized/nociplastic pain (indicated by more widespread pain on the FSQ*[135]).

Predictors of response in deep phenotyping (Aim 3). We and others have also performed QST and/or neuroimaging studies that suggest that the subgroup of cLBP patients with either neuropathic or centralized/nociplastic pain will preferentially respond to SNRIs. Yarnitsky et al. showed that the subset of neuropathic pain patients with diminished endogenous pain inhibition, measured using a conditioned pain modulation (CPM) procedure,[142] were more likely to respond to duloxetine. Our group has performed a series of studies with a different SNRI, milnacipran, and showed that the drug preferentially works in individuals with a brain imaging pattern consistent with decreased descending analgesia, namely decreased connectivity between the periaqueductal gray (PAG) and the insular cortex, as well as between the rostral part of the anterior cingulate cortex and the insular cortex.[143] We have shown that the stimulated inflammatory response (i.e., inflammation after LPS-stimulation) is strongly associated with centralized pain characteristics such as multifocal pain and the number of pain syndromes present in the MAPP study.[144,145] This appears to be true in MAPP patients with cLBP as well (see NPC preliminary data). We anticipate then that *deficient pain inhibition* on QST, *decreased PAG-insula connectivity*, and *elevated stimulated inflammatory responses* will be associated with a positive response to centrally-acting duloxetine.

18.1.5 Descriptive statistics

We will use descriptive statistics to assess data quality and characterize relationships between phenotype features prior to each treatment. In preparation for the main multivariate model-based analysis we will look at correlations between phenotype variables and responses with correlation analysis and scatterplots, analyze data for evidence of (near) collinearity between factors, study patterns of missing data, and conduct univariate analysis using models described below. The goal of this analysis is to elicit a good feel for the specific data in our team of analysts and to guide an initial approach to data reduction and predictive model trimming. Another round of descriptive model-based analysis will occur after the multivariate model-based data analysis to assess the adequacy of proposed models with model diagnostic plots and other tools.

Longitudinal data analysis. For hypothesis testing, we will use model-based likelihood ratio tests. The main hypotheses of differential treatment effects (treatment moderators, treatment effect modifiers) will be handled by introduction of the interaction terms between the phenotype and treatment indicator variables. We will base longitudinal analysis on multivariate linear and logistic mixed models with choice appropriate to the type of response variable (Logistic regression with yes/no type variables; the Proportional Odds Cumulative Logit for modeling ordinal responses; linear model and generalized linear model with continuous quantitative scores). Gaussian subject-specific intercept term will be used to model the effect of unmeasured factors shared by longitudinal observations on the same subject. While the continuous form of analgesic and secondary endpoint variables will be used in the primary line of analysis, for robustness and to gain insight into a need for specific link functions and variable transformations, we will also use binary (clinically relevant 30% and 50% improvement in analgesic responses [yes/no]) as well as ordinal form of the responses.

Best model selection. We will select best models using the unbiased Bayesian Information Criterion (BIC) and use 10-fold cross-validation to protect against overfitting the model. To deal with potentially high-dimensional phenotype variables and other demographic and clinical covariates, regularized regressions will be considered. Penalties in the likelihood function will follow the Elastic Nets family with LASSO favored for its feature elimination potential. Alternative machine-learning model-free algorithms (random forests, SVMs) will be utilized for comparison, using the binary form of the response variables.

Characterizing the predictive performance. Cross-validated and BIC-based measures of explained variation will be used to characterize the predictive potential of the continuous response models. This analysis will be supplemented with ROC analysis based on the binary form of the response variables. We will use the cross-validated and kernel-smoothed area under the ROC curve (AUC) as an appealing measure of the predictive potential with good interpretability. Order effects will be considered during secondary analysis.

Causal analysis. We will conduct exploratory analysis of causal relationships between the light and deep phenotypic factors and the analgesic and secondary response variables. We are interested in particular causal analyses potentially implicating neurobiological and inflammatory biomarkers (deep phenotyping variables) as having a mechanistic role in the mediation of the treatment effects of light phenotypic measures. Specifically, we will measure the potential mediation effect of the deep phenotype biomarkers as the proportion of the treatment effect (PTE) explained by the biomarker. PTE is represented by a relative change in the treatment regression coefficients when the biomarker is included in the model relative to the coefficient before inclusion. We will use bootstrap methods to estimate standard errors for the proportion of explained treatment effects. Wald test statistic of the form (change in regression coefficient)/(bootstrap Standard Error) will be used to test for the presence of the mediation effect.

Handling of non-study interventional procedures. Interventional procedures are different from the 4 main study treatments in that they are not subject to randomization controlled by the SMART trial and thus carry a risk of bias due to confounding by indication. We will develop causal models to deal with these effects and reduce the bias associated with these treatments to the extent possible. Interventional procedures represent dynamic treatment regimen whose initiation decision is adapted to the dynamically accumulating patient symptoms. In this situation, naïve application and interpretation of regression models correlating treatments with outcomes are misleading and insufficient for correct assessment of the treatment effect. For example, when treatment is given on worsening of the symptoms, patients receiving treatment will do worse than patients who do not, creating an appearance of treatment being harmful. We will build causal models to disentangle the learning effect of the patient history that contributed to the treatment decision from the benefit of treatment to the patient with the specific history. In doing so we will adopt the counterfactual causal inference approach. First we will construct a survival model for the time of initiation of the interventional procedure as a function of patient's history and baseline clinical characteristics. We assume no unmeasured confounding, meaning that treatment decisions are based only on the observed information. This analysis will deliver secondary results on current practices with interventional procedures. To link a treatment strategy to the expected outcome, we will use models for analgesic responses outlined above and in the Research Project. A joint model of symptom progression and its interaction with the treatment process will allow us to assess the benefit of treatment independent of a patient's symptom history.

Missing data. With high-dimensional phenotyping and the longitudinal character of the study missing data will be inevitable. Handling of missing data will include descriptive analysis of missing data patterns followed by the analysis of reasons for missingness as a nominal response using multinomial logistic regression. Sensitivity analyses will include missing data imputation by predictive-matching algorithms and missing data exclusion under a missing-at-random assumption. We do not expect more than 15% of missing data. If this assumption is not confirmed, multiple imputation approaches will be utilized.

Safety monitoring. Even though no serious side effects are expected from the treatments, in addition to the safeguards in the SMART trial of the Research Project, the Core will monitor safety periodically with 3 interim analyses and one final analysis, using the Fleming design (Fleming, T.R. (1982) One-Sample Multiple Testing Procedure for Phase II Clinical Trials, Biometrics 38, 143-151). The analysis will occur after each consecutive recruitment group of another 100 patients has completed their treatments (400 planned patients total under active treatments after drop-out).

Although it is highly unlikely that there will be extensive adverse events related to the study treatment that is any grade 2 or higher because these are all commonly used treatments for cLBP, we have established

an alarm procedure. The alarm procedure is designed to give early warning if the rate of any related AEs, grade 2 or reaches 15% or above. We will consider an alarm when more than 22, 32, 42, and 52 patients show adverse events and classify as related events and are a grade 2 or higher at the 3 interim tests and the final analysis, respectively. Events that may require the study to be discontinued or participant to be withdrawn from the study are described in Section 22.

Handling protocol deviations. Participant-specific protocol deviations will be assessed for their potential relationship to the treatment effects or the course of the disease by a medical expert. Since deviations because of safety will generally result in incomplete data on the subject, their consequences will be handled in the analysis as potentially informative missing data (as described above). Because of the difficulty of accurate determination of the relationship between protocol deviations and the treatment efficacy and the disease dynamics, several versions of the primary and secondary analysis will be undertaken:

Exclusion of the violators from the analysis population under the missing at random assumption.

1. Single (if, as expected, missing data fraction does not exceed 15%) or multiple imputation of the violator's unobserved responses using predictive matching algorithms, including the per-protocol analysis of the resultant imputed population(s).
2. With yes/no responses that have the meaning of success or failure where mixed logistic models are used per protocol, violator's responses will be classified as failures for the conservative analysis.
3. Analytic methods (2,3) applied only to violators classified as treatment or disease-related as defined by medical experts.

Power for explaining treatment effects. Consider a regression model correlating within-patient improvement due to one of the 4 main treatments with a phenotypic variable. Using a two-sided test for correlation at 5% significance level we conclude that we will have the power of at least 86% to detect correlation of 0.3 or higher, conservatively assuming the model is applied to one randomized treatment segment with 100 patients. This corresponds to first phase or second phase treatment in one of the 4 treatment groups, and a model based on the light phenotyping patient group of 400 total. Similar analysis for the smaller subgroup based on 40 patients with available deep phenotyping for a specific treatment and segment shows that correlation of 0.43 or higher will be detectable with 81% power. This is well within reach as evidenced by available literature on the association between treatment effects and phenotype variables. For example, mindfulness and pain responses showed correlations of 0.43-0.51 in prior reported studies. Our previous studies of the association between pain centralization and analgesic responses in knee OA showed similar or higher correlations.

Power for prediction. We expect that at least 30% of patients will show 50% improvements in analgesic outcomes under each of the treatments. We expect the predictive panel of light phenotypic variables to show AUC exceeding a clinically relevant AUC of 0.7, dependent on the specific setting. Under this assumption we will have the power of at least 91% to reject the null hypothesis AUC of 0.5 by a two-sided test in the subgroup analysis setting described above. With the panel including the deep phenotyping variables we expect to be able to reach a better AUC of 0.8 or higher. However, the analysis is based on smaller size of the subgroup (40 vs. 100). This results in the power of at least 89% for a similar test of AUC.

Go/no-go decisions to recommend model-based predictor panel for future clinical use. We are targeting a high sensitivity of the predictive panel of 80%. Under this scenario, the cross-validated ROC curve will be kernel-smoothed, and the decision threshold will be determined from the smoothed data to meet the 80% sensitivity. Under a normal approximation to the panel score distribution for patients who show 50% improvement and the ones who do not, in the hypothetical scenario of the above power calculation, we assess that the expected specificity value at 80% sensitivity will be around 50%. To provide guidance at the end of the study as to whether the panel is worth recommending for use in the clinical setting, worth a further study or non-promising, we will consider the overall rate of correct decisions. With the targeted sensitivity and specificity and the expected pain improvement rate in the subgroup, we are expecting that the decision will be at least 41%

correct overall. We will consider the assay not useful if it has the true overall correct decision rate of 25% or less. Dependent on the outcome, the panel will be potentially considered worth of further pursuit in the sense of potentially doubling the sample size in a future study and having a non-ambiguous decision at the end with Type I and type II errors of 5% each. Using the Fleming sequential testing design we conclude that with less than 13 correct predictions of improvement under treatment at the end of the current study the panel will be considered not worth pursuing. With 21 or more correct decisions, the biomarker will be considered clinically relevant, and with the number of correct decisions between 13 and 21, we will consider the biomarker worth of further study.

18.2 Deep Phenotyping- Data Analysis/Statistical Methods

18.2.1 Overview

This study will focus on identifying mechanistic predictors of treatment response in cLBP. We will use QST, fMRI, and measures of inflammation and ANS function to identify key neurobiological markers of cLBP that can be used *a priori* to infer what treatments are likely to work in different participant endotypes. In exploratory analyses, we will also examine changes in neurobiological markers following treatment. These analyses will help us to determine how these treatments uniquely affect pain mechanisms, a critical step for the development of new efficacious analgesics.

18.2.2 Preliminary Analysis of NPC Data

Prior to the primary analysis (primary treatment outcome will be *PROMIS Pain Interference)* descriptive statistics will be used to characterize the NPC measures, including aspects of data quality. Summary statistics for all key variables will be produced. All data will be passed to the Informatics Core, that need to be combined with self-report and behavioral measures from the BPC (assessing treatment response), for multivariate analyses and building of predictive models. The NPC will also identify high priority variables based on preliminary analyses. For instance, network-whole brain connections associated with pain subtypes (high centralized pain) that meet family-wise statistical correction or stimulated inflammatory markers/QST metrics that show robust associations with clinical characteristics, will be noted. The NPC will also help identify neurobiological markers that are supported by previous work (e.g., DMN-insula connectivity).

We will also conduct exploratory analyses to examine the mechanism of action of specific treatments. Changes in connectivity, QST, inflammatory and ANS patterns following each of the phase 1 treatments will be performed using paired sample t-tests.

We will measure the potential mediation effect of biomarkers (e.g., QST, inflammatory markers, fMRI measures) as the proportion of the treatment effect explained by the biomarker (change in the treatment regression coefficients when the biomarker is included in the model). For all models, we will use appropriate interaction terms to model effect modification. We will use bootstrap methods to estimate standard errors for the proportion of explained treatment effects, and Wald tests to evaluate the mechanistic (mediation) effect. Handling of missing data will include analysis of reasons for missingness using multinomial logistic regression. Sensitivity analyses will include missing data imputation by predictive-matching algorithms and missing data exclusion under a missing-at-random assumption.

19 Human Subjects Protections

19.1 Potential Risks

Overall, subjects taking part in the current study will be exposed to risks that are felt to be similar to those encountered in a standard clinical practice and would be deemed as having no more than a moderate risk level. The potential risks are described below and rated in terms of severity (*Table 8*) and likelihood of Occurrence (LOI) as defined in Table 5. The likelihood of occurrence is a composite measure of 1) the likelihood that a potential cause results in a hazardous situation, and 2) the likelihood that the hazardous situation results in harm. The LOI reported below is the score AFTER all identified controls have been put in place to mitigate risk.

Table 5 Likelihood of Occurrence Index (LOI)

Category	Description
Frequent	Occurrence of harm almost certain during the life of the product; History of harm resulting from failures exists from previous or similar designs
Probable	Occurrence of harm reasonably expected to occur during the life of the product
Occasional	Occurrence of harm may occur during the life of the product
Remote	Occurrence of harm unlikely to occur during the life of the product
Improbable	Occurrence of harm unexpected during the life of the product; History shows no occurrences of harm resulting from failures in previous or similar designs

Potential Risk – Breach of confidentiality. A breach of confidentiality will be considered a "definitely related" Serious Adverse Event. As such, it will be reported to the IRB within 7 days of occurrence, and a remediation plan will be put in place immediately.

Potential Risk - Blood draw. There is a slight risk of developing a small hematoma (bruise) at the site of the blood draw. There is a lot a slight risk of the patient passing out due to a vasovagal response with the blood draw.

Potential Risk – Discomfort associated with assessment questions. Some of the questionnaires can be considered personal in nature as they query about medical, symptom, and psychological well-being. Any participant becoming distressed while completing questionnaires will be encouraged to seek clarification from the local research staff at the study site or if any questions are unclear or troubling. All participants are told that they have the option to skip troubling questionnaire items and terminate participation without penalty and/or will be assisted in arranging medical/ psychiatric help including, if necessary, emergency treatment.

Potential Risk- Discomfort associated with Pro-Diary- Accelerometer - Ecological momentary assessment (EMA). Risks of completing ecological momentary assessments (EMAs) on the PRO-Diary (wrist-worn monitor) include discomfort, frustration, and the potential hassle of interruption of daily routine. These risks will be minimized by allowing participants to initiate the wake- and bed-time assessments when it is convenient for them and by allowing participants to opt-out of or postpone EMAs that are not convenient for them (they will be shown how to silence the monitor/delay reporting). These risks will also be minimized by keeping the assessments as brief as possible. Participants may also experience discomfort from wearing the PRO-Diary, especially if they are not used to wearing a watch on a daily basis. This risk is extremely rare in our experience collecting data. We will minimize this risk by offering participants choices of wrist band types and by telling them that it may take a few days to get used to wearing the PRO-Diary.

Potential Risk - Treatment Interactions – PainGuide. All participants will continue to receive care from their physician of record throughout the study. During the 6-week run-in period, all individuals will be given access to an online self-management resource, but this is a "therapist-less" intervention and therefore no additional contact is made with the participant except for initial orientation to the website. This program has been provided to patients for years with no recorded adverse events. Nonetheless, patients are always informed to contact study staff with any concerns or questions.

Potential Risk – Discomfort associated with the self-management intervention. The self-help interventions could cause emotional discomfort in as much as participants are asked to monitor their symptoms and create plans for better pain control and functionality. We expect negative effects to be extremely rare given that the behavioral self-management techniques included in PainGuide have been available to the public for over 10 years and have been embedded in efficacy trials by us and other researchers with few or no adverse effects.

Potential Risk – Treatment Interactions – Physical Therapy and Exercise. The overall risk to participants is minimal. The most likely risk is the temporary increase in muscle soreness, mild pain, or temporary fatigue from the physical therapy treatment. The physical therapy visit also involves self-report assessment of history

and symptoms to help tailor the treatment. We have summarized the risks in the Table 6 below, and provided additional detail in the accompanying text.

Table 6. Summary of Risk Profile

Procedure	Risks	LOI	Seriousness
Physical therapy -- Manual therapy, joint mobilization, directional preference exercises	Muscle soreness	Occasional	2
	Back pain	Occasional	2
	Fatigue	Occasional	2
	Bruising	Improbable	1
Self-Report of Medical History & Symptoms	Psychological distress	Improbable	1-3

Physical therapy includes a manual therapy component which may cause temporary mild muscle soreness and increase in pain due to physical manipulation by the therapist. For the vast majority of people, these symptoms subside within 2 hours of treatment and many people report feeling better after the treatment is applied. The exercises may cause temporary fatigue. There are no known long-term risks associated with participant in the proposed research as many of the task-specific

Self-Report of Medical History & Symptoms: The thoughts and feelings that go along with having chronic back pain might be magnified by having to answer personal questions about one's condition. In particular, answering questions about one's health condition and function might contribute to feelings of despondency.

Potential Risk - Treatment Interactions – Mindfulness-Based Stress Reduction. While MBSR is a behavioral intervention generally regarded as safe, clinically significant adverse events have been reported from engaging in mindfulness practices (e.g., feelings of derealization, exacerbation of psychiatric symptoms or clinical deterioration). During MBSR, participants will meet weekly with the psychotherapist delivering the intervention, who will monitor for clinical worsening of depression and other psychiatric symptoms, including any self-harm or suicidal ideation or intent, and will continue to receive care from their physician of record throughout the study. In addition, participants will engage in light stretching or yoga poses that may cause temporary mild muscle soreness. Furthermore, patients are always informed to contact study staff with any concerns or questions.

Potential Risk – Treatment Interaction – Acupressure. Self-acupressure is a safe intervention. From our previous 3 clinical trials over the past 10 years using this acupressure point formula, we have observed no serious adverse events associated with the study intervention. Our most recent and largest trial of self-acupressure in fatigued cancer survivors (N=288),[63] had 6 adverse events related to acupressure, and all were non-serious cases of mild bruising at acupressure sites. There are no known long-term risks associated with self-acupressure. To minimize the chances of bruising, participants will be trained by the acupressure instructor in how to apply the correct amount of pressure with the AcuWand. Specific attention will be paid to not apply too much pressure. The AcuWand has a built in "buzzer" to notify the study participant when the correct amount of pressure is reached, which will minimize chances of bruising. Phone calls will also be made to the participants for the first 2 weeks of self-acupressure by the study coordinator to monitor progress and answer questions. The participant is free to withdraw from the intervention at any point if the self-acupressure intervention becomes uncomfortable.

Potential Risk – Duloxetine. Duloxetine will also be administered as it typically would be by an experienced provider, again focusing on slow gradual dose escalation. Participants will be warned about the most common

side effects with this drug include nausea, vomiting, nausea, dry mouth, constipation, diarrhea, fatigue,difficulty sleeping, dizziness, light-headedness, mood swings, sexual dysfunction, and rarely, allergic reaction. All of these side effects are thought to be less common with slow gradual dose escalation, and many (especially gastrointestinal intolerance) typically get better over time. The most serious adverse effect associated with duloxetine, and one which causes us to modify our exclusion criteria for the entire study, is the increased risk of suicidality with initiation of this drug, especially in individuals under age 25. Thus, we exclude individuals under age 25 or with a history or active suicidality from participating in our MRC study. Additionally, duloxetine is a category C medication with unknown risk to fetus. Participants will be advised of this and will be asked to either abstain from sexual activities or use an acceptable method of birth control.

Potential Risk - MRI. Prior to inclusion in the study, the presence of potential MRI risks, such as pacemakers, surgical clips or metallic surgical devices will be excluded by medical and surgical history using a standard review form. The overall risk to participants is minimal. The most likely risk for is the time burden associated with completing study procedures. fMRI, DTI and ^{1}H-MRS may result in some slight discomfort from the noise produced by the MRI machine and the MRI's magnet's ability to pull metal objects toward it. This pull can cause metal objects in the body (e.g. surgical clips or staples) to move and cause bleeding or disruption of surrounding tissue. Also, claustrophobia may be problematic, and individuals will be screened for this problem. Lastly, there is some proposed risk to pregnant women receiving an MRI scan.

The MRI scans themselves are painless and not uncomfortable, although it does require the subject to lie still with the head and part of the body confined in a tunnel-like device. Fast imaging sequences, such as those employed in this study, have the potential to induce peripheral nerve stimulation (PNS). PNS can be described as a light touching sensation on the skin surface and may cause mild discomfort, but is not harmful to the patient. Other than those described above, there are no known biological risks due to exposure to the magnetic fields such as those that will be utilized in this study.

Potential Risk – Pheno Device.

Risk	LOI	Severity	Mitigation
Slight low back muscle fatigue or soreness the following day similar to a light workout	Occasional	1	Participants will be instructed to move as fast and as far as they can COMFORTABLY. Researchers will be trained on all study procedures to protect participants.
Exacerbation of pain symptoms or condition following the motion assessment if the participant is a back pain patient		3	Participants will be instructed to move as fast and as far as they can comfortably. Researchers will be trained on all study procedures to protect participants. Researchers will make it clear from the beginning of the study that participants can stop participating at any time. This will help ensure that anyone experiencing any type of discomfort will not be motivated to complete the study despite their best health interest.

			Participants will not be permitted to participate until inclusion/exclusion criteria are assessed and satisfied. Patients will not be permitted to participate until they have been cleared by one of our researcher clinicians. Patient participants will conduct research visits in a clinical environment under close supervision.
Irritation, pinching, rubbing, or sticking of skin from harness components	Improbable	2	Participant touching materials use fabrics and materials that are standard in clothing.
Participant loses balance when performing motion test and falls	Improbable	3	Participants will be instructed to move as fast and as far as they can comfortably. Researchers will be trained on all study procedures to ensure participant safety. Patient participants will conduct research visits in a clinical environment under close supervision.
Breach of Confidentiality	Improbable	3	The software has undergone a risk assessment by UMHS IT and has been approved to store PHI.
Cross contamination of infectious element between patients	Improbable	3	The device will be cleaned thoroughly using hospital-grade sanitizing wipes after each use. Participants will wear the motion sensor harness over their clothing to avoid contact with skin.
Allergic reaction to harness materials	Improbable	3	Participant-touching materials do not contain latex and use fabrics and materials that are standard in clothing
Electrical leakage from IMU sensors resulting in shock	Improbable	1	Motion sensors are an off the shelf product that have been made for wearable human use. Motion sensors are battery powered, encased in plastic, and are low voltage devices. The harnesses are constructed of electrically insulating materials, providing an additional layer of protection. The charger system has a product safety mark.

			Device will be evaluated by UMHS Clinical Engineering to be within the prescribed tolerance for patient contact.
Participant piercings or other wearable materials (e.g. insulin pump) snag during motion testing	Remote	2	Software will include instructions and researcher user training to instruct participants to remove or secure all wearables that could snag during motion prior to testing.
Sensors interfere with performance of other devices, including medical devices	Improbable	2	Sensors are tested to Federal Communications Commission for Bluetooth Transmission standards and the IMU sensors' Bluetooth signal is similar to that of a wireless mouse or headphones. Device will be evaluated by UMHS Clinical Engineering to be within the prescribed tolerance for patient contact.

19.2 Potential Risks Associated with Deep Phenotyping

Potential Risk – Quantitative Sensory Testing (QST) Pressure delivery devices, including the MAST stimulator, manual algometer, pinprick, and rapid cuff inflator (used before and during MRI) may result in temporary discomfort and areas of skin indentation and/or reddening that resolves within minutes to a couple hours. These risks are deemed to be "common" but not serious to the patient. Although uncommon, some participants have reported mild tissue/muscle tenderness lasting for up to one day following testing. In rare cases, minor bruising has been reported following pressure stimulation. This resolves in a few days. The two-point discrimination aesthesiometer, the cold water used for CPM, and the M-VAST visual stimulus may also result in transient discomfort that usually resolves in a few seconds to a couple minutes after the test stops. Additional possible discomfort of the visual stimulation task may be headache or nausea while or after performing this task.

Potential Risk - MRI. Described in Section 19.1.

Potential Risk - Back Maneuvers (performed before and during MRI). Patients will undergo a series of exercise maneuvers designed to temporarily increase their low back pain. Previous studies have determined that this increase is on average 34% above baseline and that the duration of exacerbation is less than one hour. However, while no adverse events related to this pain exacerbation have been previously reported, there remains a chance that this pain provocation will last more than one hour.

Potential Risk – Autonomic Nervous System Monitoring (BIOPAC system). The BIOPAC System used for ANS monitoring is non-invasive and MRI-compatible. ECG and respiratory signals will be acquired with two transcutaneous leads (i.e., electrodes) placed above and below the heart and a pneumatic belt placed just below the rib cage. GSR, PPG and temperature will be acquired transcutaneous leads placed on the fingertips of the index and middle fingers. Skin irritation may occur due to skin cleaning and prep (e.g., with alcohol pads), conductive gel, adhesives and materials utilized to affix leads to the subject's skin; however, we anticipate this will rarely occur. We also do not anticipate that any sensations will occur from the recordings. Risks associated with these measures are minimal since they are non-invasive. However, some participants

may experience anxiety and/or a general unease associated with unfamiliar physiological testing and/or when applying or removing sensors

19.3 Adequacy of Protection Against Risks

All patients enrolled in this study will complete an informed consent document which will be approved by the University of Michigan IRBMED. The informed consent interview is conducted by the study staff and includes a verbal and written explanation of the study, including the purpose, testing procedures, time commitment, inclusion/exclusion criteria, risks and benefits, alternative treatments, confidentiality, compensation, study personnel contacts, use of genetic material for research, and required regulatory information. All individuals are given the opportunity to ask questions. Once all questions and concerns are addressed to the participant's satisfaction, the participant signs the consent form.

During the process of obtaining informed consent, participants will be reminded that their responses to questionnaires are confidential and that they may refuse to participate in the project and/or withdraw at any time without any penalty or loss of benefits. All study staff will have completed and passed certification in the proper and ethical handling of consent and participation in human research (e.g., CITI training) to further ensure the proper treatment of individuals participating in this study. The signed informed consent document is stored securely and separately from all other research materials.

19.4 Protections Against Risks

Breach of confidentiality. Several measures have been taken to reduce the risk of breach of confidentiality. These include training of study team members, electronic and physical security measures for data capture and storage, and collecting a minimum of identifiable information for each individual. The study team will take all possible steps to protect the privacy of subjects. This includes:

1. After processing by the biorepository, samples will not be labeled with the subject's name or other easily identified numbers (like social security numbers or date of birth)
2. Subject's samples will be coded (assigned a unique study ID number) which will allow the researchers to link the sample to other information such as questionnaires and other study data.

Discomfort Associated with Assessment Questionnaires. Any participant becoming distressed while completing questionnaires will be encouraged to seek clarification from the local study staff or if any questions are unclear or troubling. All participants are told that they have the option to terminate participation without penalty and/or will be assisted in arranging medical/ psychiatric help including, if necessary, emergency treatment. Staff will have emergency contact procedures in place (established SOPs) should this type of assistance be needed.

Discomfort Associated with EMA and Pro-Diary. Risks associated with EMAs and Pro-diary will be minimized by allowing participants to initiate the wake- and bed-time assessments when it is convenient for them and by allowing participants to opt-out of or postpone EMAs that are not convenient for them (they will be shown how to silence the monitor/delay reporting). These risks will also be minimized by keeping the assessments as brief as possible. Participants may also experience discomfort from wearing the PRO-Diary, especially if they are not used to wearing a watch on a daily basis. This risk is extremely rare in our experience collecting data. We will minimize this risk by offering participants choices of wrist band types and by telling them that it may take a few days to get used to wearing the PRO-Diary.

Discomfort Associated with the non-pharmacological interventions. Participants may withdraw from the study at any time and this will in no way affect their medical care. In the rare event that an adverse event (AE) occurs associated with the conduct of the interventions, the local study staff will be available to assist participants. Study staff will also be trained in how to reach medical care within each clinical site should additional care be needed. There are established protocols for study staff including flowcharts for decision making and addressing various AEs such as an adverse response to the intervention (e.g., worsening pain) or the disclosure of serious psychiatric symptoms (e.g., suicidal ideation, psychotic episode). The PIs and study

coordinators will ensure appropriate follow-up to any AE and the event will be reported in accordance with the UM IRBMED.

Discomfort Associated with Physical Therapy. Participants will be asked to report to the treating therapist about what is causing pain or fatigue and can stop as needed. Participants will be given instructions in symptom relief following treatment such as using an ice pack. They will also be asked to report any pain increase lasting more than 2 hours to the treating therapist at the next visit. The PT program is designed to facilitate movement and to not exacerbate the condition, but all reports of higher symptoms will be discussed to determine if any modifications need to be made.

Blood Draw: The amount of blood collected from participants is limited, consistent with the guidelines established by the University of Michigan IRBMED (i.e., 15cc's). Collection is done in a sterile manner to decrease the risk of infection and performed by trained medical personnel who will apply pressure to the withdrawal site to prevent the possible development of a hematoma. Study team will also be trained to address any patients with vasovagal symptoms.

Laboratory Samples and Inflammatory Marker Analysis: Samples will be stored in a de-identified manner and linked to other phenotyping data only by anonymous subject ID number. Patients are informed during the informed consent process that they will not be offered the results of any laboratory testing as all analyses will be performed on an anonymous dataset.

MRI. To minimize the risk from the MRI, participants will complete and sign a safety screening form provided by the University of Michigan and will be instructed to bring or wear clothing without metal fasteners, and remove jewelry and any other metal objects from their body. All people (including staff) who enter the exam room that contains the magnet are hand screened for magnetic material before entering. Also, participants will wear foam earplugs or headphones to reduce the loud noises made by the scanner. Participants will be able to communicate with the examiner throughout the scan. If needed, the participant will be removed immediately from the scanner. During deep MRI sessions, participants will be monitored at all times by research personnel associated with the project or the investigators themselves. They will be encouraged to contact the study team if they notice any unusual symptoms or untoward side effects. The investigators have extensive prior experience in the utilization of MRI for research. The MRI machine is operated within FDA guidelines so the potential for inducing PNS is low. Women of childbearing potential will be required to take a urine pregnancy prior to MRI. If refused, the participant will be excluded from MRI portion of the protocol.

19.5 Protections Against Risks Associated with Deep Phenotyping

Quantitative Sensory Testing. Methods to reduce risks associated with QST (as conducted before and during MRI) will include the following: a) the proposed settings and methods are widely used and have been shown to be safe in extensive use worldwide; b) participants are told that they are free to stop any testing procedure at any time; c) research personnel receive extensive training and follow detailed standardized operating procedures that ensure safety, d) the maximum applied pressure intensities are set to be below levels that would cause tissue damage; e) the MAST automated pressure stimulators include redundant software, electrical, and mechanical safety features to ensure that the amount of pressure applied does not cause tissue damage, including a button that the patient or researcher can push to immediately release the device from his/her thumb; f) the maximum illuminance of the visual stimulus does not cause eye pain or eye injury; g) the lowest temperature of the cold stimulus (6°C) is not tissue damaging; h) testing is automatically stopped if participants report severe pain or discomfort (e.g., 100 on 0 to 100 scale).

MRI. Described in Section 19.4.

Back maneuvers. This procedure will be supervised by the study team, and the pain from this procedure is expected to be temporary. The frequency, duration, and type of maneuvers are entirely under patient control. Patients will decide which maneuvers to do and they will always have the option to opt out of this task or stop. Patients will be able to take their typical PRN pain medications (e.g., NSAIDs) after scanning, if they feel the

need. If participants still find the increased pain to be uncomfortable, the study team will discuss with them other self-management techniques they could use to reduce their pain. We have published with this technique before[172,188] with few adverse events (none severe).

ANS monitoring: To minimize the risk of skin irritation, we will only use commercially available FDA-approved skin prep materials and disposable adhesive gel leads. A new set of leads will be used for each participant. Leads will not be attached to damaged, broken or irritated skin. Prior to placement and after removal skin area will be cleaned with alcohol pads. Participants will be instructed that they may stop participating at any time.

20 Potential Benefits of the Proposed Research to Research Participants and Others

Individuals assigned to any treatment arm of the study may directly benefit in terms of enhanced pain management from having access to self-management materials and non-pharmacological and pharmacological interventions. In addition, there is considerable potential benefit to future patients with chronic low back pain should this trial support the effectiveness of these alternative of opiate-based pain treatment and elucidate their underlying mechanisms. Section 13 describes the incentive payment schedule for participants.

21 Importance of Knowledge to be Gained

For patients with chronic low back pain in the United States, opioids remain a common but often counter-beneficial clinical option. Alternatives are known to be efficacious, but they are often not implemented in routine clinical care given skepticism, logistical, and resource-related barriers. In this context, the findings from this study will provide rigorous evidence regarding the effectiveness of these interventions and the underlying mechanisms. The risks in this study are reasonable in relation to the importance of knowledge to be gained in service of improved pain management.

22 Study and Participant Discontinuation

22.1 Study Discontinuation

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, NIAMS and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor 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.

The interventions evaluated in this study are all tested and considered standard treatment for cLBP. Thus, there is no foreseeable possibility that any of these interventions could result in the termination of the study. A safety concern unrelated to our study is the potential spread of COVID-19 and a mandated shutdown of our study by either the university or the state of Michigan. Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

22.2 Participant Discontinuation

Participants may withdraw voluntarily from the study or the PI may discontinue— a participant from the study. In some cases, a participant may withdraw from the study intervention—or be discontinued from the study intervention by the PI(s)—and still continue to participate in other aspects of the study. If the participant no longer meets the inclusion/exclusion criteria for the study, they may be withdrawn. For example, the participant becomes pregnant or is diagnosed with cancer.

If a participant chooses to withdraw from an intervention and they can still continue participation in the study. They will be asked to come in for the remaining study visits and complete the mini-assessments.

22.3 Lost to Follow-Up

A participant will be considered lost to follow-up if they fail to 3 consecutive study visits. Study staff will attempt to contact the participant 3 times after every missed visit.

23 Data Safety Monitoring Plan (DSMP)

The study team will conduct scheduled assessments of the study progress monthly for the first six months and then on a semi-annual basis. Adverse events will be reported according to FDA guidelines and will be sent to the University of Michigan IRBMED. The DSMP is described in a separate document (see DSMP).

23.1 Definitions, Collection and Reporting of Adverse Events (AEs), Serious Adverse Events (SAEs) and Unanticipated Problems (UaP)

23.1.1 Adverse Event (AE)

An AE will be defined as any unfavorable or unintended change in structure, function, signs, or symptoms temporally associated with the conduct of this study whether or not a causal relationship with the study has been established. The participants will be asked to spontaneously report any AE Date of onset and resolution (if applicable) of the AE will be documented. The PIs will monitor all AEs to the termination of subject involvement in the study or to a satisfactory resolution if the AE is ongoing.

Events will be considered study-related if classified by the PIs as definitely not, probably not, possibly, probably, or definitely related according to the definitions in *Table 7*.

Table 7: Defining Relatedness for Adverse Events

Relatedness	Definition
Definitely Not	The event is definitely not associated with study.
Probably Not	The temporal association, patient history, or clinical condition is such that the study is not likely to have had an association with the observed event.
Possibly	The event: a) follows a reasonable temporal association with the study procedures, but b) could have been produced by the patient's clinical condition or other therapy.
Probably	The event: a) follows a reasonable temporal association with the study conduct, b) abates upon discontinuation of study procedures, and c) cannot be reasonably explained by the patient's clinical condition or other therapy.
Definitely	The event: a) follows a reasonable temporal association with the study, b) abates upon discontinuation of study procedures, c) cannot be reasonably explained by the patient's clinical condition or other therapy, and d) reappears on re-exposure to the study intervention/procedures.
Unknown	Not enough information exists for the assessment of causality at the time of occurrence.

Signs and symptoms will be graded by the PIs as mild, moderate, severe, or life threatening according to the definitions below (*Table 8*).

Table 8: Defining symptom severity for adverse events and potential study risks

Score	Grade	Definition
1	Mild	Causing no limitation of usual activity
2	Moderate	Causing some limitations of usual activities
3	Severe	Causing inability to carry out usual activities
4	Life-Threatening	Patient was at immediate risk of death from the event

23.1.2 Serious Adverse Events (SAE)

A serious adverse event (SAE) is defined as any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization relating to study treatment
- A persistent or significant disability/incapacity hospitalization relating to study treatment
- An important medical event based upon appropriate medical judgment

23.1.3 Unanticipated Problem (UaP) Definition

An unanticipated problem may be either an actual harmful or unfavorable occurrence or any development that potentially increased the likelihood of harm occurring in the future. Assessment Criteria:

- **Unanticipated Severity**: The nature, severity, or frequency of the event(s) or information was NOT expected, given descriptions in the study documents or the characteristics of the subject population being studied.
- **Related:** There is a reasonable possibility that the procedures involved in the research caused the problem.
- **Increased Risk:** The event(s) or information suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized (including physical, psychological, economic, or social harm).

23.1.4 Protocol Deviation (PD)

An accidental or unintentional change to, or non-compliance with the research protocol that does not increase risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data. Deviations may result from the action of the subject, researcher, or research staff. Departure from the IRB approved research protocol without prior IRB approval for the variation.

23.1.5 Expected Adverse Events

The following table describes expected adverse events in for this study (*Table 9*). Participant safety monitoring and the process of halting the study is further described in Section 22.

Table 9: Management of expected study adverse events

Expected Adverse Event	Criteria for Management	Intervention Modification, if any
Biospecimen Collection		
Bruising/Hematoma at site of draw	Participant may verbally report this.	Participant can apply ice to the area.
Discomfort with Physical Therapy		
Muscle soreness Back Pain Fatigue Bruising Psychological distress	Participant reports symptoms lasting more than 2 hours. Participant verbalizes this.	Participants can stop as needed. Modification may be made to the PT program. Modification to be determined by Physical Therapist.
Mindfulness-based Stress Reduction (MBSR)		
Feelings of de-realization, exacerbation of psychiatric symptoms or clinical deterioration. Muscle soreness or injury	Clinical worsening of depression and other psychiatric symptom. Participant verbalizes.	Will be evaluated by clinical psychologist on the study team who may refer the participant for appropriate treatment including emergency service if required. All reports of higher symptoms will be discussed to determine if modifications to the program need to be made.
Acupressure		
Mild bruising at acupressure sites	Participant verbalizes bruising.	The participant is free to withdraw from the intervention if the self-acupressure intervention becomes uncomfortable.
Duloxetine		
Nausea, vomiting, dry mouth, constipation, diarrhea, fatigue, and difficulty sleeping. Thoughts of self-harm or suicidal ideation	Participant verbalizes experiencing.	Study doctors will evaluate the participant. Participants have the option to stay on lower dose or stopping the medications. Participants may be referred for appropriate treatment including emergency services if required. Participation can also be discontinued if there is active suicidal ideation.
Quantitative Sensory Testing		
Residual Soreness at testing site Headache, nausea	Participants displaying sustained pain over 48 hours post testing.	Participants will be allowed to take NSAIDs. Stimuli duration and timing may be reduced. Follow up visual stimulation may be omitted or reduced at the follow up visit.

	Participant verbalizes residual headache, or nausea.	
Autonomic Nervous System Monitoring (BIOPAC)		
Irritation to the skin Anxiety or general unease	Participant verbalizes Participant verbalizes	Participants will be instructed they can stop participating at any time. Follow up autonomic nervous system monitoring may be omitted.
MRI		
Claustrophobic Discomfort from noise		Participants may stop the session at any time. The follow up visit may omit the MRI session.
Pheno Device		
Slight low back muscle fatigue or soreness the following day similar to a light workout Exacerbation of pain symptoms or condition following the motion assessment if the participant is a back pain patient	Participant verbalizes Participant verbalizes	Participants will be instructed to move as fast and as far as they can COMFORTABLY and can stop at any time. Researchers will be trained on all study procedures to protect participants. Patient participants will conduct research visits in a clinical environment under close supervision.
Participant loses balance when performing motion test and falls		
Cross contamination of infectious element between patients		The device will be cleaned thoroughly using hospital-grade sanitizing wipes after each use. Participants will wear the motion sensor harness over their clothing to avoid contact with skin.
Breach of Confidentiality		The software has undergone a risk assessment by UMHS IT and has been approved to store PHI.
Allergic reaction to harness materials		Participant-touching materials do not contain latex and use fabrics and materials that are standard in clothing.

Electrical leakage from IMU sensors resulting in shock		Motion sensors are an off the shelf product that have been made for wearable human use. Motion sensors are battery powered, encased in plastic, and are low voltage devices. The harnesses are constructed of electrically insulating materials, providing an additional layer of protection. The charger system has a product safety mark. Device will be evaluated by UMMHS Clinical Engineering to be within the prescribed tolerance for patient contact.
Participant piercings or other wearable materials (e.g. insulin pump) snag during motion testing		Software will include instructions and researcher user training to instruct participants to remove or secure all wearables that could snag during motion prior to testing.
Sensors interfere with performance of other devices, including medical devices		Sensors are tested to Federal Communications Commission for Bluetooth Transmission standards and the IMU sensors' Bluetooth signal is similar to that of a wireless mouse or headphones. Device will be evaluated by UMHS Clinical Engineering to be within the prescribed tolerance for patient contact.

23.1.6 Study Events Reporting Requirements

A timeline for reporting AEs, SAEs, UaPs and Protocol deviations to the NIAMS Executive Secretary and the Institutional Review Board of the University of Michigan are described in *Table 10*.

Table 10:Timeline for Reporting Study Events to NIAMS and the IRB

Event	**NIAMS Executive Secretary who will report to the DSMB and NIAMS**	**UM IRB**
Serious Adverse Event *(Related)*	Within 48 hours of the investigator becoming aware of the event	Within 7 days of occurrence notification
Serious Adverse Event (Unrelated or Anticipated)	Within 48 hours of the investigator becoming aware of the event	Annual report to IRB prior to scheduled continuing review
Non-serious adverse events grade 2 or higher *(moderate or greater)*	All non-serious adverse events (even those graded as "mild") should be reported in aggregate as part of the routine DSMP report	Annual report to IRB prior to scheduled continuing review
Any unanticipated problems that are related to the study and	Within 48 hours of the investigator becoming aware of the event	Serious problems within 7 days of occurrence

indicate risks to subjects		Non-serious problems within 14 days
Privacy violation or breach of confidentiality	If impacting participant safety, report within 48 hours of being notified of the occurrence; all other violations or breaches of confidentiality that do not impact participant safety can be reported as part of the routine DSMP report.	Report to IRB within 7 days Within 24 hours to the UMHS Privacy Office
Protocol deviations	If impacting participant safety, report within 48 hours of being notified of the occurrence; all other deviations that do not impact participant safety can be reported as part of the routine DSMP report	Annual report to IRB prior to scheduled continuing review

23.1.7 Informing Participants of AEs and SAEs

Participants will be informed of any adverse events or serious adverse events if risk-benefit profile is impacted. Events significantly impacting the study integrity that will require a change in protocol and additionally require re-enrolling of participants. All active study participants would then be notified. Furthermore, any participant incidental findings will be shared with the PI and conveyed with participant's health care provider.

23.2 Study Governance and Oversight

23.2.1 Data Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) acts in an independent, advisory capacity to the study sponsor, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), to monitor study progress, data quality, and accumulating safety data, in order to alert the Institute regarding any potential safety or other monitoring concerns affecting the conduct of the study. The DSMB is provided access to the study protocol, consent forms, and other pertinent study related documents, in addition to comprehensive reports with study data to aid in the data and safety monitoring for the duration of the study. The board will meet at least semiannually to assess safety and efficacy data from each arm of the study. The board will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the sponsor and communications will be coordinated by the NIAMS Executive Secretary. The responsibilities of the DSMB are described below.

- Review the research protocol, Data and Safety Monitoring Plan (DSMP), and informed consent documents, including all proposed revisions. The Manual of Operating Procedures (MOP), which may contain the sections included above, is also reviewed.
- Evaluate the progress of the study on an ongoing basis, as needed, including periodic assessments of data quality, participant recruitment, accrual and retention, participant risk versus benefit, performance and other factors that can affect the outcome.
- Evaluate safety throughout the course of the study through the routine review of aggregated adverse event safety data, in addition to expedited review of unanticipated problems, serious adverse event reports, and protocol deviations/violations impacting participant safety. The DSMB Safety Officer reviews the documentation provided by the study team and makes recommendations to the NIAMS regarding protection of the participants.
- Evaluate proposals of new sites (that differ from the approved application) and make a recommendation to the NIAMS as to whether the enrollment at the site(s) is expected to enhance overall enrollment. Activities include evaluating the patient population pool, catchment area description, recruitment plan, and target enrollment for any new clinical sites.

- Consider the impact of factors external to the [study/trial] when new information, such as scientific or therapeutic developments, becomes available and may affect safety of participants, their willingness to participate in the [study/trial] or the ethics and conduct of the trial.
- Assist the NIAMS by commenting on any problems with study conduct or performance.
- Ensure that the plan for maintaining the confidentiality of the data and the results by the investigative team is appropriate.
- Review and evaluate requests for protocol modifications.
- Review data after completion of each cohort to approve dose escalation.
- Review in advance of the study initiation the specific stopping rules and plans for interim analyses as established by the PI and selected members of the study team. These plans outline the conditions under which the trial may be stopped (e.g., difficulties in recruitment, retention, obtaining outcome measures, or other issues).
- Review the interim analyses and/or accumulating data at the specified interval(s), and as appropriate and make a recommendation to continue, terminate, or modify the [study/trial] based on observed benefit or harm in accordance with the planned stopping rules

24 Quality Control Procedures

24.1 Staff Training

All staff will complete CITI Good Clinical Practice (GCP) training and read related study documents. Training will also include shadowing 5 individuals being enrolled and enrolling 5 individuals under supervision.

24.2 Standard operating procedures (SOPs)

SOPs will be updated throughout the study with versions and saved to folder on the server. Where possible, SOPs will be built into the electronic data capture system. Peer reviewing process will occur with paper documents and will be followed with a check list to eliminate any errors. The correction process will be listed out in detail in the SOP for peer reviewing

24.3 Site Monitoring

Site monitoring is described in Section 25.

24.4 Reports

Reports will be supplied from REDCap database at any time throughout the study to review overall study progress, including regulatory matters, recruitment, adverse events, data quality, and to review any interim analyses.

25 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), within Good Clinical Practice (GCP) guidelines, and with applicable regulatory requirement(s).

While NIAMS may decide to request a site visit or remote site visit be conducted by the NIAMS Executive Secretary at any point during the course of the study. The study team will be responsible for the day-to-day routine clinical monitoring.

For the first 6 months, a comprehensive review of data will take place monthly by the study team for targeted data milestones and semiannually for targeted data verification of endpoint, safety and other key data variables. The distribution of monitoring reports will coincide with monthly targets and annual reviews. After the first 6 months, reviews will be done on a semi-annual basis and will include the random review of 10% of the data. Findings will be captured in a monitoring report and reviewed with the study team. Corrective actions will be taken by the study where possible and staff re-training maybe considered if more than 10% errors are found in the data.

Intervention fidelity will be collected for the study arms on a quarterly basis and documented. If more than 10% errors are found, staff will be retrained to improve data quality.

26 Publications

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

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

27 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. The study leadership in conjunction with the NIAMS Executive Secretary 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.

28 Abbreviation Glossary

Adverse Event (AE)

Back and Pain Center (BPC) – The back and pain center clinic that is located at 325 E Eisenhower in Ann Arbor Michigan. Houses the division of pain research team who is conducting the BACPAC study

Case Report Form (CRF) – A printed, optical, or electronic (eCRF) document designed to record information about study participants.

Clinical Research or Study Coordinator (CRC) – An individual that handles the administrative and day-to-day responsibilities of a clinical trial. This person may collect or review data before it is entered in the study database.

Code of Federal Regulations (CFR) – An annual compilation of rules and regulations published in the Federal Register by the executive departments and agencies of the Federal Government.

Coordinating Center (CC) – A group organized to coordinate the planning and operational aspects of a multi-center clinical trial. CCs may also be referred to as Data Coordinating Centers (DCCs) or Data Management Centers (DMCs).

Conflict of Interest (COI) – A conflict of interest occurs when individuals involved with the conduct, reporting, oversight, or review of research also have financial or other interests that may be affected by the results of the research.

Chronic Lower Back Pain (cLBP)

Chronic Pain and Fatigue Research Center (CPFRC) – Research unit in charge of carrying out the DEEP phenotyping visits for patients are interested and eligible.

Data and Safety Monitoring Board (DSMB) – An oversight body that is independent of the study investigators, and is appointed by the NIAMS to monitor participant safety and data quality, and to assess clinical trial progress.

Data and Safety Monitoring Plan (DSMP)

Food and Drug Administration (FDA) – An agency within the U.S. Department of Health and Human Services (DHHS), responsible for protecting public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, nation's food supply, cosmetics, and products that emit radiation.

Good Clinical Practice (GCP) – Section 2 from the International Council for Harmonisation provides guidance for good design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials to ensure data and results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule – Public Law 104-191 provides for the protection of personal health information. The Privacy Rule, Title II of the Act, regulates the way certain health care groups, organizations, or businesses, called covered entities under the Rule, use and disclose individually identifiable health information known as protected health information (PHI). Title II also establishes that covered entities ensure the security and privacy of PHI.

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) – An independent body consisting of medical, scientific, and non-scientific members whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, protocols and amendments, and of the methods and materials to be used to obtain and document the informed consent of trial participants.

International Conference on Harmonisation (ICH) – An international collaboration between the United States, the European Union and Japan to harmonize the testing requirements of pharmaceutical products intended for human use. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. Harmonisation is achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side.

Investigational New Drug Application (IND)/Investigational Device Exemptions (IDE) – An IND is the means through which the Food and Drug Administration (FDA) grants the sponsor permission to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application (21 CFR 312).

An IDE allows the investigational device to be used in a clinical trial to collect safety and effectiveness data for human use (21 CFR 812).

Lower Back Pain (LBP)

Mindfulness-Based Stress Reduction (MBSR)

Manual of Operating Procedures (MOOP)/Manual of Procedures (MOP) – A "cookbook" that translates the protocol into a set of operational procedures to guide study conduct. A MOOP/MOP is developed to facilitate consistency in protocol implementation and data collection across study participants and clinical sites.

Not Applicable (NA) –When recording data on a study form, if the information is not applicable, then the acronym NA should be used to fill out the field.

Not Available (NAV) – When recording data on a study form, if the information is not available, then the acronym NAV should be used to fill out the field.

Not Done (ND) – When recording data on a study form, if the evaluation required for a field is not done, then the acronym ND should be used to fill out the field.

Observational Study Monitoring Boards (OSMBs) – A body independent of the investigators that is appointed by the NIAMS to provide ongoing review for an observational study. The OSMB closely monitors data acquisition for comprehensiveness, accuracy, and timeliness as well as and monitoring participant safety and confidentiality.

Office for Human Research Protection (OHRP) – A federal government agency within the Department of Health and Human Services (DHHS) charged with the protection of human subjects participating in government-supported research. The OHRP issues assurances to institutions reviewing human subjects research and oversees compliance of regulatory guidelines by research institutions.

Principal Investigator (PI) – The individual with primary responsibility for achieving the technical success of the project, while also complying with the financial rules and requirements, administrative policies, and regulations associated with a grant or award. Although Principal Investigators may have administrative staff to assist them with the management of project funds, the ultimate responsibility for the management of the research project rests with the Principal Investigator.

Physical Therapy (PT)

Quality Control (QC) – The internal operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of trial related activities have been fulfilled (e.g., data and form checks, monitoring by study staff, routine reports, correction actions, etc.).

Quantitative Sensory Testing (QST)

Serious Adverse Event (SAE)

Safety Monitoring Plan (SMP) – A plan that outlines the oversight of a clinical trial.

Safety Officer (SO) - The Safety Officer is an independent individual, usually a clinician, who performs data and safety monitoring activities in low-risk, single-site clinical studies. The Safety Officer advises the NIAMS Program Director regarding participant safety, scientific integrity and ethical conduct of a study.

Standard Operating Procedure (SOPs) – Detailed written instructions to achieve uniformity of the performance of a specific function across studies and patients at an individual site.

Unanticipated Problem (UaP)

Unknown (UNK)- When recording data on a study form, if the information is unknown, then the abbreviation UNK should be used to fill out the field.

29 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.

Version	Date	Description of Change	Brief Rationale

30 References

1. Medicine Io. Relieving pain in America a blueprint for transforming prevention, care, education, and research. In. Washington, DC: National Academy of Sciences; 2011.
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