BACPAC Statistical Analysis Plan

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Trial Statistician	Alex Tsodikov and Kelley Kidwell
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1 SAP Signatures

I give my approval for the attached SAP entitled **BACPAC SAP** dated 09-Oct-2025

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Date: _____

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Name:

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Date: _____

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Signature: 

Date: _____

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2 Abbreviations and Definitions

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

Back Pain Consortium Research Program (BACPAC)

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)

Patient-Reported Outcomes Measurement Information System (PROMIS)

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.

Sequential, Multiple Assessment, Randomized Trial (SMART)

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.

Treatment Assignment Tool University of Michigan (TATUM)

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.

3 Introduction

3.1 Preface

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.[1] 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. 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.

At present there are data suggesting a variety of structural/mechanical, neural, psychological, cognitive, behavioral, social, and economic contributors 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. 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.

3.2 Study Scope and Objective

The objective of this study is to establish a cohort of cLBP patients in order to conduct a pragmatic clinical trial of four cLBP treatments. Rich phenotypic data will be collected for each patient which will allow investigators to assess which evidence-based cLBP treatments are most effective for different cLBP patient subpopulations.

4 Study Aims and Endpoints

4.1 Study 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 enrolled in a Sequential, Multiple Assessment, Randomized Trial (SMART) and randomized to a series of treatments, including: a) mindfulness-based stress reduction (n=102), b) physical therapy and exercise (n=102), c) acupressure self-management (n=102), or d) duloxetine (n=102). 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 common cLBP therapies. We will leverage the SMART design to perform the most comprehensive study-to-date of currently available predictors for commonly used cLBP therapies. All patients enrolled in 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 functional neuroimaging, quantitative sensory testing, plasma measures of inflammation, and autonomic tone.

4.2 Statistical Analysis Objectives

The above study objectives have been translated into the following statistical analysis objectives:

Objective 1: Assess differential treatment response using the light and deep phenotype data.

Objective 2: Given a patient phenotype, identify the best initial treatment for the patient.

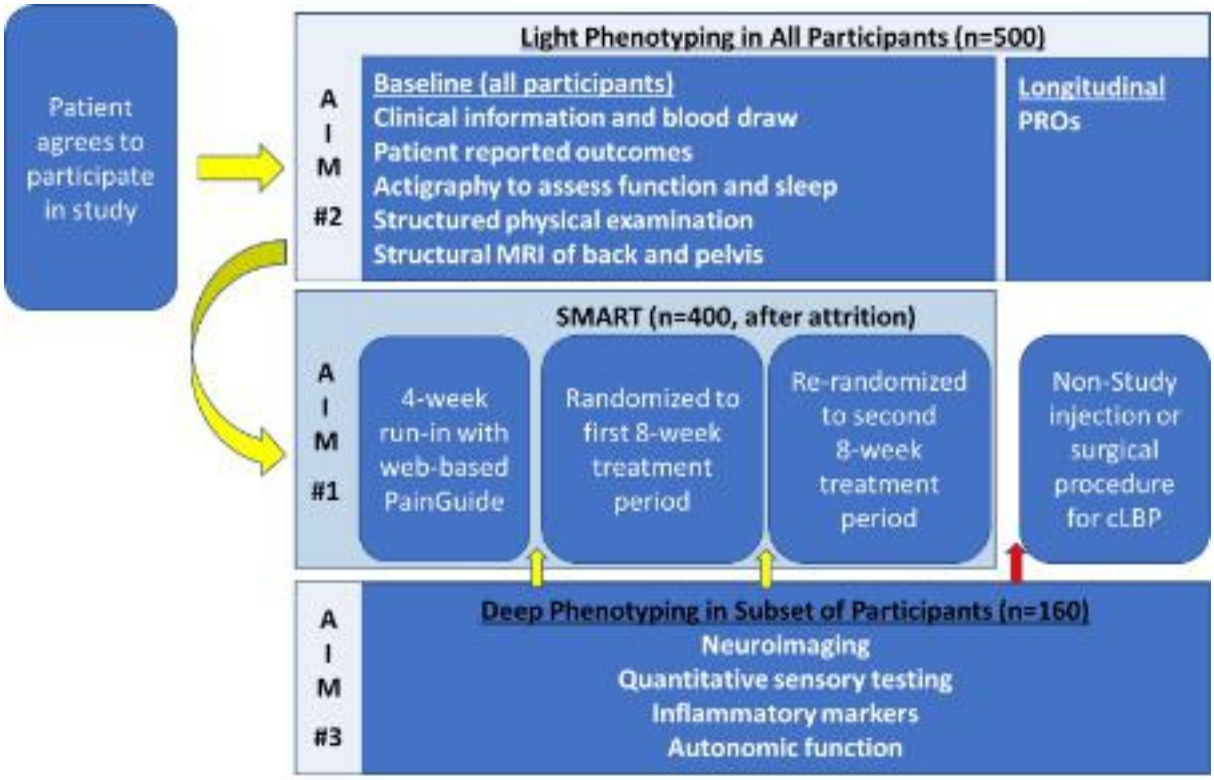
Objective 3: Identify the mechanisms that explain the causal treatment effects.

4.3 Endpoints

The primary study endpoint is the change in the PROMIS (Patient-Reported Outcomes Measurement Information System) pain interference score between the T2 pre-intervention visit and T3 post-intervention visit. The PROMIS pain interference measures the degree to which a patient's pain interferes with the patient's life. The survey questions assess interference in different domains including work around the home, recreational activities, and social activities. A univariate pain interference score is calculated from the respondent's answers. This process is described in Section 9.2.

The study's secondary endpoints consist of the change in the Pain Intensity (PEG) and the Patient Global Impression of Change (PGIC) between the T2 pre-intervention visit and T3 post-intervention visit. The other exploratory PROMIS measures will include a measure of physical functioning, fatigue, sleep disturbances, and cognition. The process of computing each secondary endpoint from survey responses is found in Section 9.2.

Figure 1 Study aims and overview



5 Study Methods

5.1 General Study Design and Plan

We will conduct a 36-week pragmatic trial in a cohort of cLBP patients (see Figure 1 and Figure 2). 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 a total of approximately nine months.

At baseline (T1), approximately 500 patients will undergo a comprehensive baseline phenotyping assessment. After receiving PainGuide (access to an online self-management program) for 4 weeks, each participant will complete a light phenotyping assessment (T2) and a subset of these patients (n=160) will complete an additional deep phenotyping assessment. Those who still have significant pain interference (≥2 from Patient Global Impression Scale, PGIC) will be randomized to one of the four 8-week long interventions (i.e., Mindfulness-Based Stress Reduction (MBSR), Physical Therapy (PT)/Exercise, Acupressure self-management [eHealth app], or Duloxetine). Participants with a PGIC=1 will not be randomized and continue with long-term follow-up. The PainGuide run-in is designed to provide the lightest "touch" intervention and to help control for regression to the mean. We will use block randomization with random block size of 4 and 8. Approximately 102 patients will be assigned to each treatment group including Physical Therapy/Exercise, MBSR, Acupressure, and Duloxetine treatment groups. For addition details, please see Section 6.3.

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 still having significant pain interference (≥2 from Patient Global Impression Scale [PGIC]) will be re-randomized to receive one of the three treatments they did not receive in the first treatment period. Participants with a PGIC=1 will not be randomized and continue with long-term follow-up. 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 interim assessments that take place at 2-week intervals in between the regular assessments (T1-T5).

The study aims to identify which interventions are most efficacious for different patient phenotypes. The primary analysis will explore how treatment response depends on patient phenotype. Secondary analyses will compare dynamic treatment regimens by patient phenotype. The SMART study does not include a control group because the efficacy of the four treatments has already been shown for the population of cLBP patients.

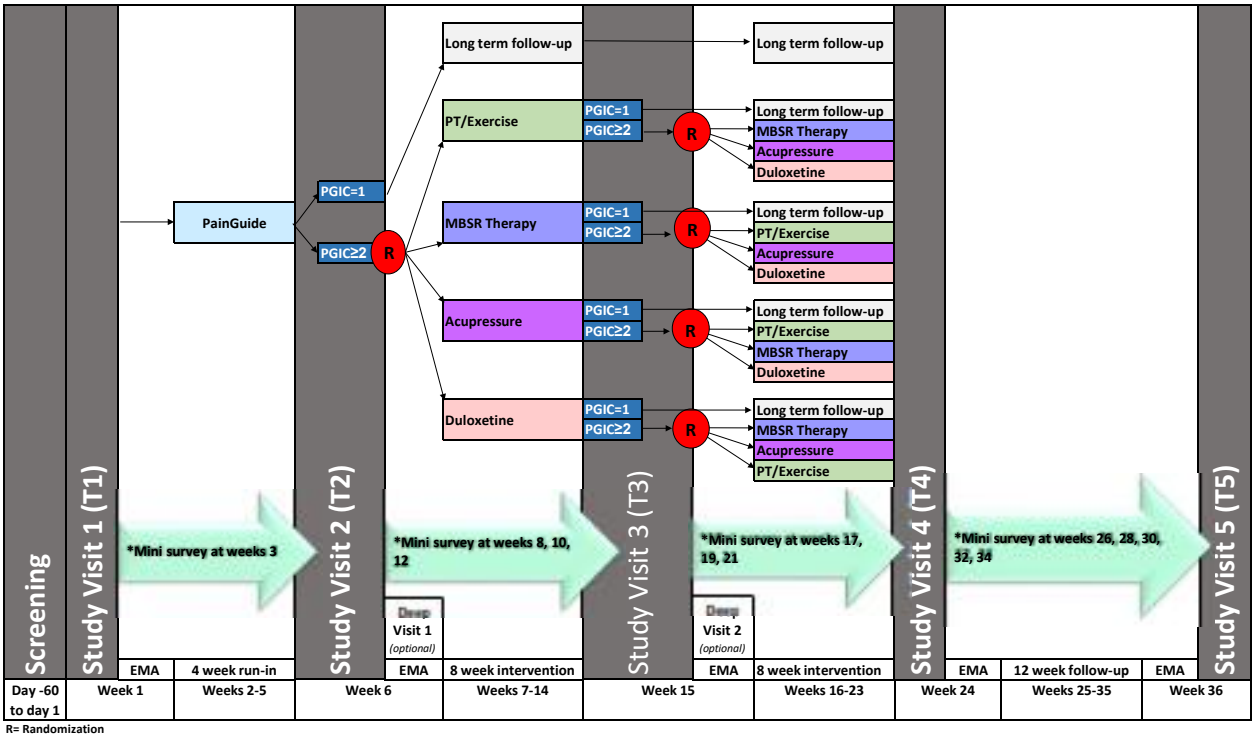
Study team members will not be blinded to patient treatment assignment.

5.2 Deep Phenotyping

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 the first

treatment.

Figure 2 SMART Study Diagram Including Assessment Strategy



5.3 Description of Study Treatments

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 still have significant pain interference (PGIC≥2) will be randomized to one of four 8-week treatments: a) Mindfulness-Based Stress Reduction (MBSR), b) Physical Therapy and Exercise (PT), c) Acupressure Self-management, and d) Duloxetine.

5.3.1 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 [2–4], 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 [4–7], although data quality is yet only fair. MBIs also improve depression, anxiety, and addiction [8–10] that often accompany chronic pain, and have been found to reduce opioid misuse in chronic pain sufferers [11–13]. 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 [2,3,14,15]. This is consistent with reports that beliefs, anticipation, and depressive and anxious states can lead to physiological amplification of pain intensity [14–16], and conversely that attentional modulation may alter pain perception [14,16]. 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 [2,3,17–19] (see meta-analysis [20]), decreases pain catastrophizing [21,22] and increases positive reappraisals.[23] Mindfulness is associated with increased activity in brain circuits involved in sensory perception (e.g. insula and dACC) during laboratory pain [17,24–26], 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 [17,19,27,28] and meta-analyses [29,30]). The pain reduction mechanism of mindfulness appears distinct from placebo and does not involve the endogenous opioid system. [17,31,32]

5.3.2 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.[33] 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 [34]. 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.[33,35] 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.[36]

5.3.3 Acupressure Self-Management

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[37]). 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 (self-applied) 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[38,39], and low back pain specifically.[40–43] 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.[44,45] 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.

5.3.4 Non-Opioid Pharmacotherapy - Duloxetine

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) that is FDA-approved for use in cLBP,[46–48] 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 descending anti-nociceptive pathways.[49]

5.4 Inclusion-Exclusion Criteria and General Study Population

5.4.1 Participants

Subjects who are ages 25-70 years and who are being seen at Michigan Medicine will be recruited.

Diversity in race and ethnicity is anticipated. All races and ethnicities will be considered for inclusion in the study. Enrollment will be defined as the number of participants consented and randomized into the 4 treatment arms. This study will enroll 408 participants (up to 102 into each intervention) and it is expected that approximately 500 participants may be consented to meet enrollment. Enrollment will be stopped when this enrollment goal is met.

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

5.4.2 Inclusion Criteria for Light Phenotyping

- We will use the definition of chronic low back pain (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.[50]
- Individuals must have a pain interference score of ≥60 on PROMIS Pain Interference at T1 for inclusion. The normal population mean and standard deviation for the PROMIS Pain Interference measures are 50 and 10 points, respectively. Therefore, 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.

5.4.3 Exclusion Criteria for Light Phenotyping

- History of discitis osteomyelitis (spine infection) or spine tumor
- History of 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 receiving disability or compensation within the past year, or 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.

5.4.4 Contraindication to study interventions

5.4.4.1 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

5.4.4.2 Acupressure

- Currently receiving acupressure or acupuncture through a formal therapy

5.4.4.3 MBSR

- Current participation in a structured MBSR program

5.4.4.4 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

5.4.5 Contraindication to MRI

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

5.4.6 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

5.4.7 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

5.5 Randomization and Blinding

Blocked randomization will be used for the randomization schedule. Block size will be randomized between 4 and 8 and the ordering of treatment assignments within a block will be random. Randomization will be performed without stratification. Study recruitment will continue until 408 patients have been randomized into a treatment group at study phase T2. We expect that it will be necessary to recruit approximately 500 patients into the study in order to achieve the target of 408 SMART participants. Based on our previous studies [51–53], we expect that approximately 15-20% of patients recruited at study phase T1 will not enter the SMART at study phase 2 due to either response to the PainGuide self-management intervention or withdrawal from the study.

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. The randomization software will also track study treatment-allocation progress and provide documentation of the treatment assignment.

Randomization at T3 will be done similar to the one at T2.

Due to the nature of the study and its interventions, neither patients nor study staff will be blinded

to patients' treatment assignments.

5.6 Study Assessments

Table 1 shows the schedule of assessments for screening, demographic data, outcomes, and light and deep phenotyping. Measurements at T2-T5 may occur within a target observation window around each nominal study sample time (±2 weeks). A subset of 160 eligible subjects enrolled in the clinical trial will undergo deep phenotyping.

Table 1 Schedule of Assessments

	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 Saliva		x																	
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		x			x				x								x			

Force Minimum Dataset*																			
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

6 Sample Size

The study aims to continue randomizing patients with cLBP to initial treatment until 102 randomized patients per group are available for the analysis (i.e. completed their T1-T4 visits and had PGIC≥2 at T2). This is the target patient group. Based on assumed attrition rates we expect the total number of consented patients to be over 500. Attrition rates include patients who are not randomized because their pain was "very much improved" after run-in (PGIC=1 at T2). Such patients will still be included in the analysis with their limited data. The power analysis, however, excludes these patients because effects in the randomized participants are of primary interest. The smaller subgroup based on 40 patients will be from the target patient group for deep phenotyping for specific treatments.

6.1 Power for explaining treatment effects

Consider a regression model for correlating within-patient improvement (primary: change in PROMIS Pain Interference; secondary: change in PEG, PGIC; many others as exploratory, see below for details) 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 80% to detect correlations of 0.28 or higher, conservatively assuming the model is applied to one randomized treatment segment with 102 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 target patient group of 408 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 0.42 or higher will be detectable with 80% 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 osteoarthritis showed similar or higher correlations.

7 General Analysis Considerations

7.1 Timing of Analyses

Three interim analyses (safety endpoints) and one final analysis (primary and secondary endpoints) will be conducted. The interim analyses will occur after each consecutive group of another 102 evaluable patients has completed their treatments (408 target group patients total under active treatments after drop-out). The final analyses will be conducted after the 408 target group participants have completed their respective planned visits.

7.2 Analysis Populations

7.2.1 Full Analysis Population

Patients completing their run-in and at least one follow-up visit make up the full analysis population. For purposes of analysis patients who are not randomized are still considered as assigned to "long-term follow up" "treatment" and part of the analysis population. The focus of the model-based analysis though will be on the parameters coding for the effects among the randomized patients. Some will be randomized once, some twice, some not at all, dependent on the PGIC status. Intent to treat is defined as a prospective list of treatment assignments at T2 and T3 conditionally on patients' all possible longitudinal PGIC status values at those visits. This collection by the PGIC status makes up the patient's assignment list. Assignments are generated for each recruited patient who completes the run-in (T1 and T2) prospectively. Actual treatments may deviate from the dynamic treatment regimen (when not on the specific patient's assignment list). The primary analysis will be done under

the intent-to-treat framework using the treatment assigned to each subject instead of the treatment that each subject may have actually received.

7.2.2 Per-protocol Population

The per-protocol population will include all subjects who remain in the study to time T4 and are judged to have been compliant with their assigned treatments. Descriptions of treatment compliance are found in Section 9.5 in Table **4**. A sensitivity analysis restricted to the per-protocol population will be done to assess differences between actual vs intended treatment effects.

7.2.3 Safety Population

The safety population includes all patients who enter the study at study period T1. Safety analyses will use the safety population to assess the rate of adverse patient events. Safety analysis will be done based on adverse event rates for the whole safety population regardless of their treatment assignments or actual treatments.

7.3 Covariates and Subgroups

Since the purpose of the study is to identify patient subgroups that differentially respond to the four treatments, our analysis will explore many treatment-covariate interactions. Table **2** and **3** list the expected treatment modifiers, which are the primary covariates of interest, for the light and deep phenotype measures, respectively. The light phenotype table also describes each variable's expected mechanistic role (treatment modifier versus treatment mediator). For additional details, please see Section 18.1 of the UM BACPAC clinical trial protocol.

Table 2 Hypothesized light-phenotyping treatment modifiers.

Phenotypic variable	Expected treatment-phenotype interaction	Mechanistic Role
Patient pain catastrophizing score	MBSR	Moderator
Patient experience score	MBSR	Mediator
Fear avoidance beliefs score	PT/Exercise	Mediator
PROMIS self-efficacy score	PT/Exercise	Moderator
Fibromyalgia Screening Questionnaire	Acupressure	Moderator
Biologic Sex	Acupressure	Moderator
Fibromyalgia Screening Questionnaire	Duloxetine	Moderator
PainDETECT score	Duloxetine	Moderator

Table 3 Hypothesized deep-phenotyping treatment modifiers.

Deep Phenotype variable	Measurement Modality	Expected treatment-phenotype interaction	Mechanistic Role
Subgenual ACC activity	fMRI	MBSR	Moderator
Ventrolateral PFC activity	fMRI	MBSR	Moderator
S1 activity	fMRI	MBSR	Moderator
Thalamus activity	fMRI	MBSR	Moderator
Baseline activity	Actigraphy	PT/Exercise	Moderator
Parasympathetic tone	Heart Rate Variability	PT/Exercise	Moderator
Vagal Tone	EKCG and PPG	PT/Exercise	Mediator

High Basal Inflammation	Blood Sample	PT/Exercise	Moderator
Pain Threshold	QST	Acupressure	Moderator
Posterior Insula Glutamate	H-MRS	Acupressure	Moderator
Insula-DMN connectivity	fMRI	Acupressure	Moderator
DMN-SI connectivity	fMRI	Acupressure	Moderator
Deficient Lower Back Pain Inhibition	QST	Duloxetine	Moderator
Lesser PAG-Insula connectivity	fMRI	Duloxetine	Moderator
Elevated Stimulated inflammatory response	Blood Sample	Duloxetine	Moderator

We plan to conduct a single subgroup analysis that will assess whether males and female differentially respond to the proposed treatments.

In addition to the covariates listed above, the following biological variables will be controlled for in the primary analysis: sex, age, BMI, race, and education.

7.4 Missing Data

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. The focus of the descriptive analysis will be to assess associations between treatment assignment and data missingness. We will compare analyses conducted with missing data imputation and missing data exclusion under a missing-at-random assumption. These sensitivity analyses will assess the degree to which mechanism underlying the data missingness affects the findings of the study. Missing data imputation will be conducted using predictive-matching algorithms. We do not expect more than 15% of data to be missing. If the rate of data missingness is greater than 15%, multiple imputation approaches will be utilized in the primary analyses.[54]

7.5 Multiple Testing

We will not formally control for multiple comparisons since the aim of this trial is to identify cLBP patient phenotype and treatment combinations for future study. Additionally, we would have little power to identify significant phenotype-treatment interactions with multiple testing procedures due to the study design (16 possible SMART treatment pathways, 12 dynamic treatment regimens and n=408 patients) and heterogeneous patient phenotypes. Results will be presented using confidence intervals and standardized treatment effect sizes rather than p-values. We will additionally employ cross-validation schemes when appropriate to assess the degree to which phenotype-treatment interactions generalize out-of-sample.

8 Summary of Study Data

A CONSORT flow diagram (Appendix A) will compare how the study unfolded with the pre-trial plan to include information about the number screened, the number enrolled, the number randomized to each intervention at each stage of the trial, final completion rates, and the number of individuals in analytic datasets.

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 collinearity between factors, study patterns of missing data, and conduct univariate analysis using models described below. The goal of the data summarization 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.

At first, all intervention groups will be combined. Any variable that requires creation from collected data will be coded and created for examination. Continuous variables will be summarized by minimum, maximum, arithmetic mean, median, and standard deviation at each time point. Histograms and boxplots will be used to assess distributional characteristics of baseline and follow-up variables. The outcomes will be summarized and plotted at each time of assessment to assess distributional characteristics. Categorical variables will be tabulated with frequencies and percentages. The number and percentage of missing observations for all variables will be reported for each variable at each time point for the entire sample. Missingness for the primary and secondary outcome variables will be assessed by intervention group to evaluate any differential missingness.

We will then describe the patient population by initial intervention group to construct a table describing the baseline characteristics of each intervention group. The table will include baseline characteristics, baseline medical history, and baseline values of primary and secondary outcome variables. Significance testing of baseline characteristics between groups will not be performed based on statistical and CONSORT recommendations.

8.1 Subject Disposition

A patient will be considered to have reached stage *t* after they complete the patient reported outcome forms within the specified stage *t* window. A subject will be considered to have dropped out of the study at stage *t* if they progressed to the prior stage but fail to complete the patient reported outcome forms within the stage *t* window. Whenever possible, the reason for each subject's dropout will be recorded. See Protocol for details concerning the timing of study assessments.

The full analysis population consist of all subjects who complete the patient reported outcome forms at stage T2 at the end of the run-in phase. The full analysis population size will be a count of these patients. The per-protocol analysis populations will consist of all patients who remain in the study and are complaint with their treatment assignments during the first and second treatment periods. The per-protocol population sample size will equal the number of patients who complete the study to stage T4 and are compliant with treatment. Treatment compliance is defined in Section 9.5.

Subjects will be recruited into the study over the course of 2.5 years. Target recruitment rates vary by month based on historical recruitment averages at the BPC. On average, the study aims to recruit 10-15 subjects per month.

8.2 Derived variables

The study's primary and secondary endpoints are each scored as recommended by instrument authors. The PROMIS-based measures will be derived in Qualtrics using a tool released by HealthMeasures.net. The PROMIS composite scores have a population mean and standard deviation equal to 50 and 10 points, respectively. The Oswestry Disability Index is calculated by summing the individual item scores (values ranging from 0 – 5) and multiplying by 2. Its range runs from 0 to 100.

8.3 Protocol Deviations

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's departure from the IRB approved research protocol without prior IRB approval for the variation. Missing data are part of protocol deviations and may lead to exclusion from the per-protocol analysis population.

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 (see Section 8.4). Due 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:

1. Exclusion of the violators from the analysis population under the missing at random assumption.
2. If missing data fraction exceeds 15%, multiple imputation of the violator's unobserved responses using predictive matching algorithms, including the per-protocol analysis of the resultant imputed population(s).
3. 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.
4. Analytic methods (2,3) applied only to violators classified as treatment or disease-related as defined by medical experts.

8.4 Demographic and Baseline Variables

The following patient-level variables will be collected at T1 and will be treated as demographic variables during the primary and secondary analyses. There are no planned transformations of the baseline variables.

- Age
- Sex
- Gender identity
- Ethnicity
- Race
- Education level
- Employment status
- Marital status
- Household size

Summary statistics will be produced in accordance with section 9.

8.5 Treatment Compliance

Treatment compliance for each of the four study treatments is defined below in Table **4**.

Table 4 Compliance standards for treatments

Treatment	**Compliance Standard**
MBSR	Completion of 4 out of 8 sessions
PT/Exercise	Completion of 80% of PT sessions

Acupressure	Completion of 70% of the 30-minute sessions.
Duloxetine	Compliance will be assessed by counting pills returned to research pharmacy.

9 Analysis Plan

9.1 Objective 1 Analysis Plan

Objective 1: Assess differential treatment response using the light and deep phenotype data.
The main hypotheses of Objective 1 will be addressed by fitting a joint regression model the primary pain outcome (PROMIS pain interference score) at time point T3 which gains efficiency by incorporating observations at time point T4. The purpose of this analysis is to demonstrate that clinical measures are capable of predicting differential responsiveness to the four cLBP treatments. This analysis will assess the degree to which the clinicians' hypothesized treatment modifiers predict differential treatment response. Testing the differential treatment response hypotheses will be handled by including treatment-phenotype interactions in the model. The analysis will be repeated for the secondary pain outcomes (Pain intensity (PEG) and Patient Global Impression of Change (PGIC).

9.1.1 Light Phenotyping Analysis

Let $Y_{ti} \in \mathbb{R}$ denote subject i's PROMIS pain interference score at time $t \in \{2, 3, 4\}$. Let R_i denote response status at T3. Let A_{ti} be a vector denoting treatment assignment, such that the first through 4th elements represent PT/Exercise, MSBR, Acupressure, and Duloxetine treatment status. The vector X_{2i} contains the baseline covariates for subject i at time 2 (sex, age, BMI, race, and education) and Y_{2i}. For $t \in \{2, 3\}$, the matrix Z_{ti} will hold subject i's time t measurements of the hypothesized treatment modifiers. Z_{ti} will have 7 total columns that correspond to the hypothesized treatment modifiers, and the columns will be specified such that the element-wise product $A_{ti} \cdot Z_{ti}$ represents the 8 hypothesized treatment-phenotype interactions.

We jointly model data at T3 and T4 to gain efficiency in estimating the main effects of treatment, the main effects of the potential moderators, and the interaction effects between treatment and the potential moderators in stage 1. The main effects of treatment and covariates are allowed to differ between stages, but we assume these effects are additive. In contrast, treatment–by–phenotype interaction effects are assumed to be the same across both stages. We propose the following model:

$$E[Y_{3i}] = {X_{2i}}^T\beta_2 + {A_{2i}}^T\phi_2 + {Z_{2i}}^T\varphi_2 + (A_{2i} \circ Z_{2i})^T\psi_2$$

$$E[Y_{4i}] = {X_{2i}}^T\beta_2 + {A_{3i}}^T\phi_2 + {Z_{3i}}^T\varphi_2 + {R_i}^T\left[{A_{3i}}^T\phi_{3R} + {Z_{3i}}^T\varphi_{3R}\right]$$
$$+(1 - R_i)^T\left[{A_{3i}}^T\phi_{3NR} + {Z_{3i}}^T\varphi_{3NR}\right] + (A_{3i} \circ Z_{3i})^T\psi_2$$

We will fit the model for all repeated measures (Y_{3i}, Y_{4i}) using generalized estimating equations (GEE) with a working independence covariance matrix through the R package *gee*. We will use robust standard errors for variance estimation to account for the use of repeated measures. Prior to conducting inference, we will assess the functional forms of the predictors and the validity of the assumptions required for joint stage modeling, especially the assumption of constant interaction effects across treatment stages. If the assumptions for joint modeling are violated, we will conduct the primary analysis with stage 1 data only. For inference, we additionally assume Y_{3i}, Y_{4i}) follow a multivariate normal distribution.

The clinical objective of Aim 1 is to show that patient responsiveness to treatment depends on their

phenotype. To address this aim, null hypothesis of regression coefficients will be used. We will use two-sided Wald tests to assess whether the hypothesized differential treatment responses are consistent with the clinical trial data. Let θ denote a treatment-phenotype interaction (i.e., one of the elements of ψ_2). The Wald test statistic testing H_0: $\theta = 0$ is given by $W = \frac{\theta}{SE(\theta)}$. We will reject the null hypothesis at approximately the 95% level when $|W| \geq 2$.

9.1.2 Deep Phenotyping Analysis

A second analysis will assess whether deep-phenotyping measures are also predictive of differential treatment response. The form of the model will be nearly identical to the light phenotype-based primary analysis above. The analytic plan and strategy for performing inference on model parameters is the same as stated above in 9.1.1. The primary difference between the primary and secondary analysis is the number of treatment modifiers that were proposed by investigators. As a result, the deep phenotyping-based model will include multiple treatment-phenotype interactions terms for each treatment arm (see Table 5). *Table 5 Hypothesized differential responses to treatment*

Deep Phenotype variable	Measurement Modality	Expected treatment-phenotype interaction	Mechanistic Role
Subgenual ACC activity	fMRI	MBSR	Moderator
Ventrolateral PFC activity	fMRI	MBSR	Moderator
S1 activity	fMRI	MBSR	Moderator
Thalamus activity	fMRI	MBSR	Moderator
Baseline activity	Actigraphy	PT/Exercise	Moderator
Parasympathetic tone	Heart Rate Variability	PT/Exercise	Moderator
Vagal Tone	EKCG and PPG	PT/Exercise	Mediator
High Basal Inflammation	Blood Sample	PT/Exercise	Moderator
Pain Threshold	QST	Acupressure	Moderator
Posterior Insula Glutamate	H-MRS	Acupressure	Moderator
Insula-DMN connectivity	fMRI	Acupressure	Moderator
DMN-SI connectivity	fMRI	Acupressure	Moderator
Deficient Lower Back Pain Inhibition	QST	Duloxetine	Moderator
Lesser PAG-Insula connectivity	fMRI	Duloxetine	Moderator
Elevated Stimulated inflammatory response	Blood Sample	Duloxetine	Moderator

9.2 Objective 2 Analysis Plan

Objective 2: Identify additional predictors of differential treatment response using light phenotype data.

This exploratory analysis will assess whether additional patient reported outcomes captured in clinical settings can improve the prediction of differential treatment response. First, we will assess the functional forms of the predictors through univariate summaries and assess multicollinearity through pairwise Spearman correlation coefficients. Then, we will fit regularized regression models for the primary pain outcome (PROMIS pain interference score) using observations from time points T3 and T4. We will utilize adaptive elastic net (AENET) to induce variable selection while accommodating groups of correlated predictors. Given the exploratory nature of this objective, that

trial patients may have just failed other treatments prior to entering the study, and the need for as much data as possible for the proposed methods, we will treat observations from time points T3 and T4 as independent rather than as repeated measures and adjust for potential effects of stage 1 treatment on observations at T4. We will consider the selection of a treatment interaction into the model as weak evidence for treatment effect modification, and we will conduct hypothesis testing for strong evidence of treatment effect modification. The analysis will be repeated for the secondary pain outcomes (Pain Intensity (PEG) and Patient Global Impression of Change (PGIC)).

Let $Y_{ti} \in \mathbb{R}$ denote subject i's PROMIS pain interference score at time $t \in \{2,3,4\}$, R_i denote response status at T3, A_{ti} be a vector denoting treatment assignment for $t \in \{2,3\}$, and X_{2i} denote the vector of baseline variables for subject i at time point T2 (sex, age, BMI, race, education, and the baseline outcome). Let Z_{ti}be a vector denoting the additional (clinical/patient reported) predictors and their treatment interactions for subject i and $t \in \{2,3\}$. We assume

$$E[Y_{ti}] = {X_{2i}}^T\beta + {A_{(t-1)i}}^T\phi + I(t=4) * [R_i{A_{2i}}^T\varphi_R + (1-R_i){A_{2i}}^T\varphi_{NR}] + {Z_{(t-1)i}}^T\gamma,$$

and we apply Ridge and adaptive Lasso penalties to the main effects and treatment interactions of the additional predictors. That is, we estimate model parameters by minimizing the sum of squared errors subject to the constraint $(1-\alpha)\sum_j \widehat{w_j} \cdot |\gamma(j)| + \alpha\sum_j \gamma(j)^2 \leq t$, where $\gamma(j)$ denotes the j^{th} element of γ. We estimate the tuning parameters α and t using 5-fold cross-validation to minimize prediction error and estimate $\widehat{w_j} = |\widehat{\gamma_{ENET}}(j) + \frac{1}{n}|$, where n is the total number of T3 and T4 observations and $\widehat{\gamma_{ENET}}(j)$ represents the corresponding estimate of $\gamma(j)$ from a standard elastic net model. Lastly, we obtain AENET parameter estimates using the R package *gcdnet*.

For any treatment-phenotype interactions selected into the fitted model, we will conduct null hypothesis testing. We will use two-sided Wald tests based on standard error estimates from AENET. Using the fitted model, we will also obtain predicted outcomes under each of the four treatment options for all individuals. We will identify the treatment option which maximizes the predicted outcome for each individual and then form up to four subgroups of patients with the same optimal treatment. We will conduct descriptive analyses to compare the characteristics of these subgroups and generate hypotheses for future research based on any baseline patient phenotypes which may be useful for determining optimal initial treatment.

9.3 Objective 3 Analysis Plan

Objective 3: Identify the mechanisms that explain the causal treatment effects.

The primary analysis for the exploratory objective 3 (specific aim 2) will involve a series of mediation analyses in order to identify the mechanisms that underlie the differential treatment responses. This analysis will use light phenotyping data from T2 and the interim assessment conducted at the midpoint of the first-stage treatment period. Second-treatment stage data will not be used for this analysis. Investigators did not propose a light phenotyping-based mediator for the Duloxetine treatment. Thus, a mediation analysis based on light-phenotyping data will not be carried out for this study arm.

The study does not include a control group since each of the four therapies have been previously shown to be effective for treating cLBP. As a result, the mediation analyses will be conducted by treatment group. Within each treatment group, the proposed treatment modifier will play the role of the exposure in the mediation analysis. Hypothesized mediators were determined by the study investigators and are listed in Table 6 by treatment arm.

For example, consider the PT/Exercise treatment group. Investigators expect that individuals who both receive the PT/Exercise treatment and have lower self-perception of their own efficacy will respond better to the PT/Exercise intervention and have lower PROMIS Pain Interference scores at follow up. They believe that this effect is attributable in part to changes in the patients fear avoidance beliefs and avoidance behaviors. The mediation analysis will assess whether greater pain catastrophizing is associated with a greater reduction in fear avoidance beliefs, which leads to greater improvement in pain interference scores.

The outcome measure for each mediation analysis will be the PROMIS Pain Interference score measured at T3. The exposures and mediators will be measured at T2 and the first treatment-stage midpoint, respectively.

Table 6 Hypothesized Mediation Analyses by Treatment.

Treatment	**Mediation Analysis Exposure (X)**	**Expected treatment mediator (M)**
MBSR	PROMIS Pain Catastrophizing	Experiences Questionnaire Score
PT/Exercise	Pain Self-Efficacy Score	Fear Avoidance Beliefs Questionnaire
Acupressure	Fibromyalgia Screening Score	GSS-8

Here we present the generic model that will be used in each mediation analysis. Figure 3 shows a graphical representation of the model. Let Y_i denote the T3 PROMIS pain interference score for the i^{th} subject in a single treatment arm. Let X_i and M_i denote the i^{th} subject's measurements of corresponding exposure and mediator, measured at T2 and the first treatment stage midpoint, respectively. Note that both X_i and M_i depend on the treatment arm. The vector W_i contains the baseline covariates: sex, age, BMI, race, and education.

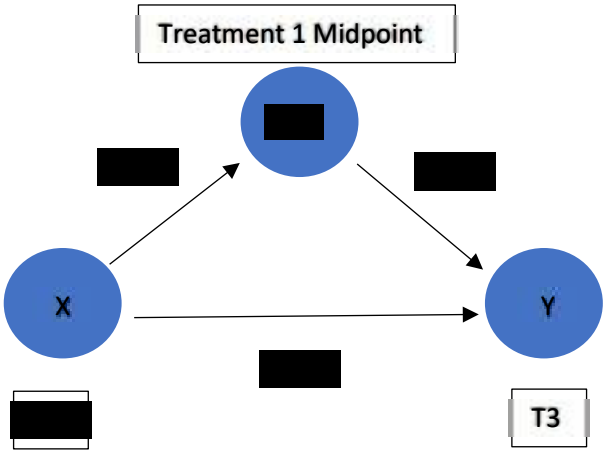
We propose the following linear models for M_i and Y_i for all $i = 1, \dots, n$:

$$M_i = \alpha_0 + \alpha_1 X_i + \phi_1^T W_i + \epsilon_{1i}$$
$$Y_i = \beta_0 + \beta_1 X_i + \beta_2 M_i + \phi_2^T W_i + \epsilon_{2i},$$

and $Cov((\epsilon_{i1}, \epsilon_{2i})^T | X_i, M_i, W_i) = \sigma^2 I$.

For this model, the so-called indirect and direct effects of X_i on Y_i are equal to $\tau_I = \alpha_1\beta_2$ and $\tau_D = \beta_1$. The "total effect" equals the sum of the indirect and direct effects: $\tau = \tau_I + \tau_D$. Whether the intermediary variable M mediates the association between X and Y is determined by assessing the evidence against the null hypothesis that the indirect effect τ equals 0. The mediation models will be fit in R using the *mediation* package [55].Inference for the indirect effect will be performed by creating a 95% confidence interval for both the direct and indirect effects[56] using bias-corrected and accelerated bootstrapping. Confidence intervals for the proportion of the total effect mediated by M will also be produced.

Figure 3 Graphical representation of the mediation models. In all analyses Y represents a patients PROMIS Pain Interference Score, while X and M depend on treatment arm.



10 Safety Analyses

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 [57]. The analysis will occur after each consecutive recruitment group of another 102 patients has completed their treatments (408 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. The standard rate is assumed to be 10%. We will consider an alarm when more than 21, 31, 41, and 51 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. If the rate of adverse events is indeed at 15% or higher, the suggestion to stop the trial will be generated by this procedure at 253 treated patients or less on average. Errors of both types are set at 5%. A decision that the rate is safe will be suggested after 265 patients on average.

Events that may require the study to be discontinued or participant to be withdrawn from the study are described in the Protocol Section 18.1.6 and Section 22.

10.1 Adverse Events

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	The event is definitely not associated with study.

Not	
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

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

10.1.1 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

10.1.2 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).

10.1.3 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.

10.1.4 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 the Protocol Section 23.

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. Participant verbalizes residual headache, or nausea.	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.
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.

10.1.5 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 indicate risks to subjects	Within 48 hours of the investigator becoming aware of the event	Serious problems within 7 days of occurrence 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	Annual report to IRB prior to scheduled continuing review

	notified of the occurrence; all other deviations that do not impact participant safety can be reported as part of the routine DSMP report	

10.1.6 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-consenting 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.

11 Other Analyses

Exploratory, we will analyze the 12 embedded dynamic treatment regimens within the SMART design using the joint model described in section 10.1.1. Additionally, we will consider further tailoring of the embedded dynamic treatment regimens using augmented outcome-weighted learning.

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13 Appendix A

BACPAC_SAP_AppendixA_Consort_8-19