0The BEST Trial: Biomarkers for Evaluating Spine Treatments

Study Protocol

Protocol Number: 00057948

National Clinical Trial (NCT) Identified Number: NCT05396014

Protocol Co-Chairs:

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1. SUMMARY OF CHANGES FROM PREVIOUS VERSIONS

Version	Date of Revision	Section(s)	Summary of Revisions Made	Rationale
2.0	4/20/2022	Title Page	Added document title	
2.0	4/20/2022	Title Page	Revised protocol chair names	Kevin Anstrom replaced Matt Psioda April 2022
2.0	4/20/2022	Title Page	Added protocol number	
2.0	4/20/2022	3	Updated Protocol Chairs and Key Personnel	Removed Derr per Derr request to avoid conflict of interest Added Rachel Goolsby as Project Manager
2.0	4/20/2022	All	Acronyms added at first mention	
2.0	4/20/22022	4.1	Objectives clarified	Per 2/11/22 DSMB request
2.0	4/20/22022	4.1	Revised duloxetine section	Revised to reflect intervention protocol changes, number of sites, and revised study launch
2.0	4/20/2022	4.1	Revised EBEM section	
2.0	4/20/2022	4.1	Revised study length	
2.0	4/20/2022	4.2	Revised schema	Corrected timing of screening call
2.0	4/20/2022	4.3	Updated Schedule of Activities	
2.0	4/20/2022	5.2	Added duloxetine exclusion criteria to risk language	
2.0	4/20/2022	5.2	Clarified and corrected risk language	
2.0	4/20/2022	8.1-8.4	Updated inclusion/exclusion criteria and contraindications	
2.0	4/20/2022	8.7	Revised recruitment strategies	Revised to account for site-specific restrictions
2.0	4/20/2022	9.2	Updated blood draw protocol	
2.0	4/20/2022	9.5	Updated imaging protocol	
2.0	4/20/2022	10.2	Updated duloxetine protocol	
2.0	4/20/2022	10.4	Updated EBEM protocol	
2.0	4/20/2022	10.5	Updated randomization methods	
2.0	4/20/2022	12.2	Clarified and corrected time points at which pregnancy status is assessed	

Version	Date of Revision	Section(s)	Summary of Revisions Made	Rationale
2.0	4/20/2022	12.3	Clarified and corrected AE, SAE, and UP definitions and reporting requirements	Per 2/11/22 DSMB request
2.0	4/20/2022	13	Clarified statistical methods	
2.0	4/20/2022	14.1	Corrected safety oversight language	Per 2/11/22 DSMB request
2.0	4/20/2022	14.1	Added data security language	
2.0	4/20/2022	14.2	Removed unnecessary listings	Per 2/11/22 DSMB request
2.0	4/26/2022	All	Revised “investigational drug pharmacy” to “approved pharmacy”	Not all sites will utilize Investigational Drug Services
2.0	4/26/2022	10.2	Revised unused pill protocol to in-person returns only	
3.0	5/27/2022	Title Page	Added National Clinical Trial (NCT) Identified Number	NCT Record created
3.0	6/7/2022	3.0	Added Anastasia Ivanova, PhD as BEST Lead Biostatician	
3.0	6/6/2022	5.2.1	Added “MRS of the spine” to description of additional imaging procedures a subset of participants may undergo	Increased clarity
3.0	6/6/2022	8.3	Clarified EBEM intervention contraindications	Split two contraindications previously combined into one bullet into 2 bullets
3.0	6/3/2022	8.4	Revised Imaging Phenotyping Contraindications	Removed two previous contraindications that are no longer being assessed and identified an additional contraindication for the spine MRS
3.0	6/3/2022	8.7	Added more specific information about ICD10 codes and keywords coordinators may use to identify participants in the EMR	Per site request
3.0	6/6/2022	9	Changed “more comprehensive spin MRI” to	The additional/deep phenotyping spine scan

			"spine MRS" and removed "longer than the required MRI" from the duration description	now only consists of the spine MRS
3.0	5/27/2022	9.2	Revised list of blood tubes collected and which blood samples are stored for possible future analyses	Corrected errors
3.0	6/6/2022	9.5	Changed "additional MRI scans of their spine" to "a MRS scan of their spine"	The additional/deep phenotyping spine scan now only consists of the spine MRS
3.0	6/7/2022	13.3	Added Safety Population and Modified Intention to Treatment Population	
3.0	5/27/2022	14.1.10	Added information about Magnetic Resonance Imaging (MRI) Quality Control	Added extra measures taken to ensure QC of MRI data
4.0	6/30/2022	4.1, 6, 7.1, 7.2, 13.1	Clarified language throughout regarding the primary outcome of the trial.	Clarification from statistical team
4.0	6/30/2022	4.1, 5.1, 7.1	Updated ordering of interventions	Clarification from statistical team
4.0	6/28/2022	4.1, 10.3, 10.3.1	Corrected duration of ESC intervention	Correction from ESC team
4.0	6/28/2022	4.1, 10.3	Changed information about texts and emails received during ESC intervention	Correction from ESC team
4.0	6/30/2022	7.1, 10.5, 13.2	Clarified that sample size simulations yield approximate results	Clarification from statistical team
4.0	7/5/2022	8.3	Added breastfeeding as a contraindication for the duloxetine intervention	ELC decision 7/6/2022
4.0	6/28/2022	10.3	Added information about Walking Program module in PainGuide	Correction from ESC team
4.0	6/28/2022	10.3.1	Removed information about ESC intervention summary module	Correction from ESC team
4.0	6/28/2022	10.3.1	Updated information about FitBit step monitoring	Correction from ESC team
4.0	6/28/2022	10.3.1	Updated numbering of ESC modules	Correction from ESC team
4.0	6/30/2022	10.5	Minimization covariates are binary yes/no	Clarification from statistical team

4.0	6/30/2022	13.3	Updated analysis populations	Clarification from statistical team
4.0	6/13/2022	14.1.10	Changed information about Magnetic Resonance Imaging (MRI) Quality Control of Brain Images	Planned human scan is not required to occur prior to scanning research participants
4.0	7/22/2022	5.2.1	Corrected language used and timeline specified in Risks Associated with Confidential Information Disclosure	
4.0	7/22/2022	9.2	Updated batch shipping schedule and timepoints	
4.0	7/22/2022	6	Corrected randomization visits specified in description of secondary objectives	
4.0	8/1/2022	9.5	Added language about imaging test scans	
4.0	8/8/2022	9.6	Updated information about Temporal Summation and Conditioned Pain Modulation tests	
4.0	9/12/2022	9	Corrected time needed for required phenotyping activities and additional phenotyping activities	Corrected discrepancy between Protocol and ICF
4.0	9/12/2022	5.2.1, 8.4, 9, 9.5	Changed “a MRS scan of their spine” back to “advanced MRI scans of their spine”	Imaging team has decided to revert to “advanced spine MRI’ terminology
4.0	9/13/2022	8.2	Updated exclusion criterion related to autoimmune disorders (increased specificity)	ELC decision 9/13/2022
4.0	9/28/2022	4.2	Corrected timing of Screening Call 2 indicated in Schema	
4.0	10/6/2022	4.1, 10.2.1	Corrected number of pills dispensed to cover longest time between visits	
4.0	10/6/2022	10.2.4	Clarified language regarding study drug shipments	
4.0	10/6/2022	4.1, 7.4	Corrected study duration	
4.0	10/7/2022	6.0	Corrected visit # of follow-up visit	
4.0	10/7/2022	8.1	Revised Run-In eligibility requirement to allow more time to watch videos and to	ELC decision 10/5/2022

			reduce the # of required response to the daily pain questions	
4.0	10/7/2022	8.3	Enhanced and clarified contraindications to ACT	
4.0	10/12/2022	9.4	Clarified language regarding additional biomechanical assessments	
4.0	10/12/2022	9.5	Corrected and clarified imaging data flow	
4.0	10/12/2022	10.1.1	Deleted incorrect language regarding missed ACT appointments	
4.0	10/12/2022	10.2	Deleted incorrect citation	
4.0	10/12/2022	10.2.6	Deleted incorrect language regarding duloxetine non-compliance	
4.0	10/12/2022	10.4.1	Clarified number of EBEM visits and expectations regarding the frequency of EBEM fidelity assessments	
4.0	10/12/2022	11.3	Corrected definition of Lost to Follow-Up	
4.0	10/12/2022	12.2	Deleted incorrect information regarding tapering duloxetine	
4.0	10/12/2022	14.1.10	Corrected timing of harmonization scans	ECL decision
4.0	10/12/2022	14.1.14	Defined order of phenotyping assessments and associated protocol deviations	
4.0	10/17/2022	10.2.1	Clarified who may conduct the physical assessments	
4.0	10/20/22	5.2.1, 5.2.3, 8.4, 9, 9.5, 14.1.14	Removed clinical spine x-ray from phenotypical assessments	Trial leadership/clinicians decision
4.0	10/20/22	9	Changed duration of required phenotypical assessments to approximately 3 to 5 hours	
4.0	10/20/22	9	Table: changed motion assessment to 20 minutes and changed basic spine MRI to 60 minutes	
4.0	10/20/22	10.4.3	Delete non-compliance definition	

4.0	10/20/22	16	Added footnote regarding piloting of NHANES Food Frequency Questionnaire	
4.0	10/20/22	5.2.1	Changed duloxetine dosage increase from gradual to increase after seven days, if no serious side effects	
4.0	10/20/22	5.2.1	Added participants who are currently breastfeeding will be excluded from duloxetine intervention	
4.0	10/20/22	7.1	Clarified the timing of the PROs and phenotypical assessments	
4.0	10/20/22	9.2	Changed timing of batch sample shipments	
4.0	10/20/22	9.4	Changed duration of additional biomechanical assessment to 50-60 minutes	
4.0	10/20/22	10.2.4	Removed log of minimum and maximum reading as a requirement	
4.0	10/20/22	14.1.3	Clarified that re-consent is allowed remotely with prior permission from DAC	
4.0	10/20/22	14.1.14	Added incorrect number of pills administered to participant as a protocol deviation	
4.0	10/20/22	Appendix A	Updated Schedule of Activities	
4.0	11/4/22	8.4	Removed hardware between T12 and S1 as a contraindication for the MRS	
5.0	2/7/23	Study Description, 7.1, 8.1, 10.4.4	Removed references to post-Run-In PEG score as an eligibility criterion	
5.0	2/7/23	7.4	Removed in-person visit requirement for discontinuation	
5.0	2/7/23	7.4	Extended study length estimate	
5.0	2/7/23	8.3	Clarified EBEM and ACT exclusion criteria for treatment overlap	

5.0	2/7/23	8.3	Added to and clarified duloxetine contraindications	
5.0	2/7/23	8.7	Added recruitment and retention referral language	
5.0	2/7/23	9.4, 9.5, 9.6, 14.1.1	Clarified language regarding participation in additional (deep) phenotyping	
5.0	2/7/23	10.2.1	Added Physical Therapists	
5.0	2/8/23	6.0	Corrected measurements informing stage 2 randomization	
6.0	4/3/2023	9, 10.2.1, 12.2, 12.3.1	Corrected references to a physical exam to instead reference the study physical assessment	
6.0	5/11/2023	8.7	Added online survey as recruitment method	ELC approval 5/10/2023
6.0	5/15/2023	10.2.6	Added instructions for duloxetine dispensation at Visit 1 for sites who ship study medication	
6.0	5/15/2023	11.2	Added safety concerns for staff as a reason to discontinue a participant	
6.0	5/31/2023	12.3.4	Added that AEs followed until resolution, stabilization, or participant is off study.	
6.0	6/15/2023	4.1, 7.1, 7.4, SOA	Removed “subset of participants” from Week 36 assessment	
6.0	6/15/2023	7.4	Removed timeframe for end of study	
6.0	6/16/2023	8.1	Removed respond to 5 emails during Run-in as an inclusion criterion	ELC decision 6/16/2023
6.0	6/19/2023	4.1, 10.2.1	Added tapering instructions for duloxetine	ELC decision 5/31/2023
6.0	6/19/2023	10.2.1	Added a reminder that study treatment will end in six weeks to 18-week phone call, in case participant would like to schedule an appointment with their provider to continue their treatment after Visit 2.	ELC decision 6/7/2023

7.0	9/1/2023	4.1, 10.2.1	Added an additional week to the tapering period at the investigator or licensed designee's discretion	ELC decision 8/23/2023

2. 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 NIAMS Terms and Conditions of Award. The study is being conducted under an NIH HEAL Initiative application.

Principal Investigators (PIs) will assure that no deviation from or changes to the protocol will take place without prior agreement from the Back Pain Consortium (BACPAC) Research Program and NIAMS (as funding agency), and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

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

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4. PROTOCOL SUMMARY

4.1. SYNOPSIS

Title: The BEST Trial: Biomarkers for Evaluating Spine Treatments

Background and Rationale:

Chronic low-back pain lasting three months or more with pain occurring on most days affects 10-20% of adults in the United States, and contributes to lost employment, disability, and, by some estimates, $100 billion in US health care expenditures annually[1-3]. In the 2010 Global Burden of Disease Survey, low back pain was ranked highest among 291 conditions in terms of years lived with disability[2,4]. Sufferers, who are disproportionately women and people with low socioeconomic status, contend with physical pain, limited mobility, and mental health symptoms[2]. Chronic low-back pain is second only to cancer in number of opioids prescribed, and opioids are the most commonly prescribed class of drugs for low-back pain, despite limited evidence of efficacy in chronic pain and the significant risks of side effects, addiction, and death.

While a broad range of treatments exists, current treatments do not adequately resolve chronic low-back pain for most patients. Systematic reviews of common treatments find small to moderate evidence to support many currently used treatments.

Research into optimum treatment for chronic low-back pain is challenging due to the diverse etiology of back pain and the varied phenotypes of back pain patients. Additional research priorities include patient phenotyping and sub-group stratification and the development of pharmacological and non-pharmacological first-line treatments for chronic low-back pain.

Through its Helping to End Addiction Long-term℠ Initiative, or NIH HEAL Initiative℠, the NIH seeks an improved understanding of the underlying biological mechanisms of chronic pain and supports the discovery and testing of novel non-addictive pain treatments to stem the ongoing opioid crisis and to support the translation of scientific findings into clinical practice[2]. BACPAC, a funded component of the HEAL Initiative℠, is a multisite consortium which will advance knowledge of the etiology and treatment of chronic low-back pain by developing an understanding of the mechanisms contributing to chronic low-back pain and identifying specific treatments or combinations of treatments that are most effective in identifiable subgroups of participants.

Study Description: The BEST Trial (Biomarkers for Evaluating Spine Treatments) is a NIAMS-sponsored clinical trial being conducted through the NIH HEAL Initiative's Back Pain Consortium (BACPAC) Research Program. Generally, this trial will inform a precision medicine approach to the treatment of chronic

low-back pain (cLBP). BEST is a multi-site, sequential, multiple assignment randomized trial (SMART) to evaluate four evidence-based interventions for chronic low-back pain. The trial is designed to meet the primary objective of estimating an algorithm for optimally assigning treatments based on an individual's phenotypic markers and response to treatment. Interventions being evaluated in this trial are: (1) enhanced self-care (ESC), (2) acceptance and commitment therapy (ACT), (3) duloxetine, and (4) evidence-based exercise and manual therapy (EBEM).

Each participant will complete an initial screening call and enrollment visit, followed by a 2-week run-in period, two consecutive 12-week treatment periods, and a 12-week post-treatment follow-up period. Upon completion of the run-in period, participant eligibility will be reassessed based on their adherence to study protocol. Participants who no longer meet eligibility criteria will be considered screen failures and discontinued from the study.

For the first treatment period, eligible participants will be randomly assigned to one of the four study interventions. For the second treatment period, depending on response to their initial treatment, participants will be randomized to one of the following treatment actions: (1) maintain their current intervention, (2) augment their current intervention with another study intervention, or (3) switch to a new study intervention. For treatment actions (2) and (3), the additional or new intervention will be randomly determined independent of participant response to the initial treatment. Specific details on these treatment actions are described in detail in Section 7.

All participants will undergo phenotyping assessments at Visit 0, 1 and 2 corresponding to baseline, the end of the first 12-week intervention period, and the end of the second 12-week intervention period, respectively. A subset of participants will undergo additional phenotyping, consisting of a more comprehensive set of phenotyping assessments, at the same visits. Section 9 provides a complete description of the phenotyping assessments.

Pain, Enjoyment of Life, and General Activity (PEG) and Patient Global Impressions Scale (PGIC) will be assessed at 6 weeks (midpoint of intervention period one), 12 weeks (Visit 1), 18 weeks (midpoint of intervention period two), 24 weeks (Visit 2), and 36 weeks post-baseline (12 weeks after intervention period two). Basic safety assessments will also be performed at these time points to assess participant tolerability to their current study intervention(s). Patients who are unable to tolerate their assigned study treatment will be educated on how to safely discontinue their current treatment plan but will otherwise remain in the study.

Objectives:

The primary objective is to estimate an algorithm to assign sequences of two cLBP treatments based on phenotypic markers and an individual patient's response to the initial treatment (*i.e.,* a dynamic treatment regime (DTR)) that optimizes effectiveness. as characterized by the primary and secondary endpoints.
The study has the following three secondary objectives:

- Estimate DTRs that optimally balance multiple outcomes, taking into account participant preferences for outcomes including pain intensity, pain interference, physical function, opioid use, depression, anxiety, sleep duration and sleep disturbance.
- Estimate DTRs that incorporate additional phenotypic markers (i.e., deep phenotyping) collected on a subset of participants.
- Assess whether effectiveness is sustained on outcomes collected 24 weeks after randomization to the second treatment.

Analyses for secondary objectives will utilize the set of primary and secondary endpoints.

The study has the following exploratory objectives:

- Evaluate the comparative effectiveness of individual treatments.
- Evaluate the comparative effectiveness of different treatment regimes (i.e., a particular regime with a given set of rules at each decision point).
- Evaluate the impact of treatment order on outcomes.

Analyses for exploratory objectives will utilize the set of primary and secondary endpoints.

Endpoints:

The primary endpoint for the study is 24-week change from baseline in patient-reported pain intensity and interference, measured with the Pain, Enjoyment of Life, and General Activity (PEG) scale.

Secondary endpoints are:

- 24-week change from baseline in pain interference, measured with the 4-item PROMIS Pain Interference scale (PROMIS-PI, 4a)
- Incidence of any opioid use at 24 weeks post baseline.
- 24-week change from baseline in physical function, measured with the PROMIS-PF Short Form 6b.
- 24-week change from baseline in depression score, measured with the PROMIS 4-item depression scale from the PROMIS 29 profile.
- 24-week change from baseline in anxiety score, measured with the PROMIS Emotional Distress-Anxiety scale (PROMIS-EDA 4a).
- 24-week change from baseline in sleep disturbance, measured with the PROMIS short form 6a.
- 24-week change from baseline in sleep duration, measured with the BACPAC sleep duration question.

Study Population:	The study will enroll adult participants who report having low-back pain for at least 3 months and on at least half the days in the past 6 months. Participants must be at least 18 years of age and meet other inclusion/exclusion criteria as described in Section 8.
Sample Size:	The study will enroll approximately 820 participants in order to obtain approximately 630 completers (i.e., 10% post-Run-in ineligibility and an additional 15% dropout rate over the course of the trial assumed). Assuming dropout occurs uniformly across study interventions, the sample size of 630 will result in having approximately 80% probability of estimating a DTR within 90% of the optimal DTR based on the study's primary endpoint. Based on previous studies, it is estimated that approximately 200 participants will consent to undergo comprehensive phenotyping (i.e., phenotyping assessments beyond what is required for all participants). More details, including assumptions regarding intervention effect sizes can be found in Section 13.
Interim Analysis:	Generally, this trial will inform a precision medicine approach to the treatment of chronic low-back pain. In order to maintain sufficient power for the precision medicine analyses, interim analyses for futility or efficacy are not planned.
Final Analysis:	Q-learning[5,6] will be used to estimate a two-stage dynamic treatment regime that assigns a sequence of cLBP treatments based on phenotypic markers and the patient's response to treatment in order to maximize the expected reduction in PEG between the beginning and the end of the study. Q-learning reduces the reinforcement learning problem of optimizing a two-stage dynamic treatment regime to a standard regression problem, after which standard regression algorithms can be applied.
Description of Sites/Facilities Enrolling Participants:	Approximately 12 U.S. sites will enroll participants into BEST; all sites are clinic settings.
Description of Study Interventions:	**Acceptance Commitment Therapy** ACT is a form of cognitive behavioral therapy that is well established for the treatment of chronic pain[7-12]. The goal of ACT is to build psychological flexibility thereby interrupting pain avoidance behavior patterns. Participants randomized to ACT will take part in 12 sessions over the course of 12 weeks. Sessions will be delivered as a combination of 4 remote face-to-face visits with a therapist and 8 therapist-supported online sessions (self-directed online modules supported by provider coaching). Online sessions will focus on helping participants accept pain, connect with negative thoughts and emotions, develop mindfulness and identify and commit to values and goals that are important to them. During face-to-face sessions with the therapist, participants will be

encouraged to share their experience of skills practice and mastery, provide examples of skill use at home, and describe what barriers they encountered.

Duloxetine

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) that is FDA-approved for use in cLBP[13], and, as such, is included as a recommended therapy in nearly all current treatment guidelines for low back pain. Study participants will be treated with duloxetine for 12 weeks during the active treatment phase. At the time of randomization, the approved drug pharmacy at each study site will dispense between 185 and 192 duloxetine 30 mg capsules and provide to participants. This will ensure enough capsules to maintain up to a 60 mg dosage through the 12-week intervention phase. A standard tapering period will occur in the 13thand 14th weeks, as needed. At the investigator or licensed designee's discretion, tapering can be extended up to the 15th week.

Enhanced Self-Care

The Enhanced Self-Care intervention will be comprised of educational modules on evidence-based cognitive-behavioral self-management skills for pain[14]. These modules will be provided digitally for self-administration over a period of 12 weeks. There will be no therapist associated with the delivery of these educational materials; however, automated text or email messages will guide participants to specific content. Everyone receives the same ESC materials for weeks 1-4, after which the text/email guidance offers personalized recommendations for accessing additional modules based upon identified problems from the baseline assessment. Additionally, the embedded walking program module will utilize Fitbit step tracking to allow participants to monitor their walking progress.

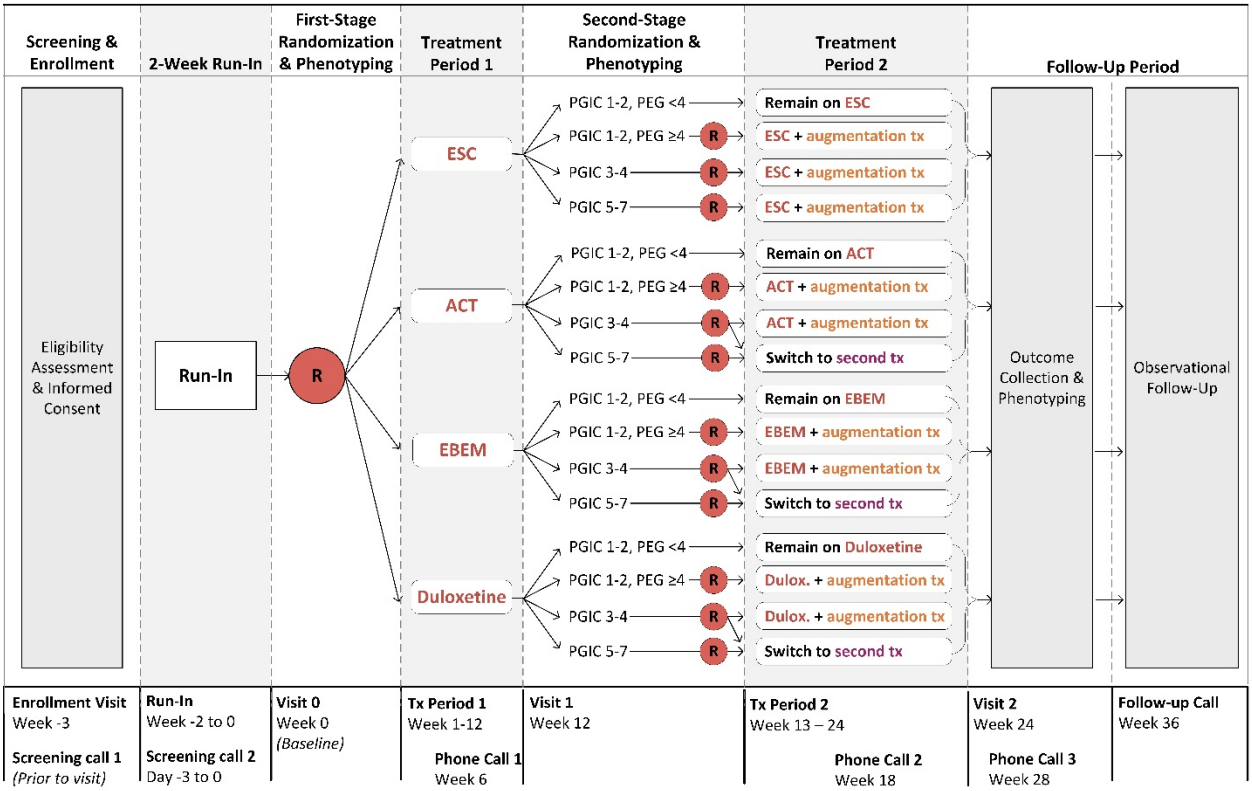
Evidence-Based Exercise and Manual Therapy

Licensed physical therapists (PTs) or Doctors of Chiropractic (DCs) will rely on evidence-based guidance to direct decision-making on the particular type of manual and exercise therapy that may be best suited to an individual study participant[15]. Special attention will be paid to the clinician's choice of language in regard to the purpose and expected outcomes of manual therapy in order to avoid enhancing catastrophizing ideations or preference for passive interventions. A total of 10 sessions will be provided over an 8-week treatment period. Two sessions per week are provided in the first two weeks followed by weekly sessions over the next 6 weeks. Treatment sessions will last approximately 60 minutes each.

Study Duration: The BEST trial will run approximately 15 months from first participant screened until last participant follow-up.

Participant Duration: The study duration for most participants will be 38 weeks. This includes the 2-week screening/run-in period, two 12-week intervention periods, and the 12-week post-intervention follow-up period.

4.2. SCHEMA



4.3. SCHEDULE OF ACTIVITIES (SOA)

See Appendix A

5. INTRODUCTION

5.1. STUDY BACKGROUND AND RATIONALE

Chronic low-back pain is a highly prevalent pain condition among adults that diminishes both physical and psychosocial wellbeing[4]. Chronic low-back pain lasting three months or more with pain occurring on most days affects 10-20% of adults[1], and 28% report back pain in the past three months[4]. Chronic low-back pain contributes to lost employment, disability, and, by some estimates, $100 billion in health care expenditures. In the 2010 Global Burden of Disease Survey, low-back pain was ranked highest among 291 conditions in terms of years lived with disability[2]. Sufferers, who are disproportionately women and people with low socioeconomic status, contend with physical pain, limited mobility, and mental health symptoms[2]. Chronic low-back pain is second only to cancer in number of opioids prescribed, and opioids are the most commonly prescribed class of drugs for low-back pain, despite limited evidence of efficacy in chronic pain, and the significant risks of side effects, addiction, and death[16]. While a broad range of treatments exists, current treatments do not adequately resolve chronic low-back pain for most patients. Systematic reviews of common treatments find small to moderate evidence for efficacy for some treatments[17-19]. In clinical practice, first-line recommendations for chronic low-back pain are often non-steroidal anti-inflammatory drugs (NSAIDS) and exercise for patients who experience non-immobilizing pain, and opioids may still be commonly recommended when other treatments have failed[20,21].

Research into optimum treatment for chronic low-back pain is challenged by the diverse etiology of back pain, the varied phenotypes of back pain patients, and difficulty assessing both the cause of pain and treatment effect. Trial design and retention issues limit our understanding of treatments and their effect. While individual trials of single or multi-modal interventions have demonstrated moderate treatment effects, heterogeneity of trial design, outcomes, and populations stymie large-scale systematic reviews[22] as well as reviews of specific treatment approaches[19]. These methodological factors highlight the need for large-scale trials with standardized measures, treatments, and outcome measures. Additional research priorities include patient phenotyping and sub-group stratification and the development of pharmacological and non-pharmacological first-line treatments for chronic low-back pain[23]. The proposed BEST trial will harmonize recruitment, enrollment, data collection, and retention strategies across multiple sites, each of which will recruit from a diverse population of chronic low-back pain patients. Drawing on expertise from within and outside of the consortium, sites will adopt ambitious recruitment and retention goals. Given historic underrepresentation of minority communities in research, the consortium will closely monitor recruitment of underrepresented communities and initiate oversampling, as needed.

The NIH supports the discovery and testing of novel non-addictive pain treatments to stem the ongoing opioid crisis and to support the translation of scientific finding into clinical practice[2]. BACPAC, a funded component of the NIH's Helping End Addiction Long-term (HEAL) initiative, is a multisite consortium which will advance treatment of chronic low-back pain by applying a precision medicine approach to identify specific treatments or combinations of treatments that are most effective in identifiable subgroups of participants.

In line with these objectives, the BACPAC consortium will conduct a multisite clinical trial, which will incorporate four interventions whose components have been studied previously and have been clinically proven to be effective for some populations. The interventions to be included in the trial are: enhanced self-care (ESC), which incorporates self-management techniques and education, acceptance and commitment therapy (ACT), duloxetine, and evidence-based exercise and manual therapy (EBEM)[10,13-15]. The trial will build on this knowledge base by applying a precision medicine approach to these proven interventions to determine the optimal treatment for specific participant subgroups. This precision medicine approach is designed to estimate an algorithm to assign sequences of two cLBP treatments based on an individual participant's changing response and phenotypic markers and may help to reduce reliance on opioids for many cLBP patients.

5.2. RISK/BENEFIT ASSESSMENT

5.2.1. KNOWN POTENTIAL RISKS

Participants taking part in this study will be exposed to risks that are viewed as similar to those encountered in a standard clinical practice and would be deemed as having no more than a moderate risk level. The following section describes specific risks associated with undergoing phenotyping assessments, receiving study interventions, and disclosure of confidential information (i.e., breaches of confidentiality).

Risks Associated with Phenotypic Assessments

Questionnaires: Questionnaires pertaining to pain, medication use, and history of chronic low-back pain and other pertinent comorbidities will be delivered as part of the study and may be considered burdensome and repetitive. Some participants may feel minor discomfort sharing information about topics such as physical health, mental health, and substance use.

Blood Draw / Venipuncture: Collection of blood is occasionally associated with minor bruising, risk of infection, discomfort, feeling light-headed, or fainting.

Stool collection: Participants will be asked to provide a stool sample which will be used to analyze gut microbiome. Stool samples may contain germs that may cause or spread infection if proper hygiene methods are not followed.

Biomechanical Assessment: All participants will receive at least one biomechanical assessment, part of which requires the use of wearable technology to assess biomechanical factors related to chronic low-back pain. Participants might find wearable technology uncomfortable and may experience light low back muscle fatigue or soreness similar to a light workout the day following the motion assessment. Less common are short-term aggravation of existing low back symptoms; irritation, pinching, rubbing, or sticking of skin from motion harness components; piercings or other wearable materials (e.g., insulin pump) snagging during the motion testing, and loss of balance while performing the motion assessment causing a fall.

Adhesive may be used to affix wearable sensors during assessments. These adhesives may cause short-term, minor skin irritation in some patients. A subset of participants will use wearable technology continuously for seven days, which participants may find burdensome. These assessments may also cause minor physical discomfort or tiredness but are unlikely to cause long-term physical discomfort.

Imaging: All participants will undergo Magnetic Resonance Imaging (MRI) of the spine. A subset of participants may undergo MRI of the brain and an additional spine MRI utilizing magnetic resonance spectroscopy. MRI is safe for most participants but is contraindicated for certain subsets of people, such as those with certain medical devices (e.g., implanted cardiac devices, cochlear implants, or intracranial aneurism clips) or with ferrous metal in their body (e.g., wire mesh, screws). MRI is not safe for pregnant women. While MRI is safe for most participants, the procedure may cause some participants to feel emotional discomfort, anxiety, and claustrophobia. The noise of MRI requires participants to wear ear protection and may cause peripheral muscle or nerve stimulation.

Quantitative Sensory Testing (QST): QST may cause minor but temporary physical discomfort. Specifically, the manual pressure algometer and pin prick stimulus are commonly used in QST studies and will not cause tissue injury at the maximum forces applied in this study. However, these instruments may cause minor physical discomfort in the areas of testing; this discomfort is expected to resolve within minutes of test completion. Conditioned Pain Modulation (CPM) assessments using cold stimuli are also uncomfortable but will be limited in intensity and duration to prevent tissue damage. The cold-water bath component of the QST assessment is contraindicated for certain participants with uncontrolled high blood pressure, heart conditions, and a history of Raynaud's Syndrome.

Genetic Analysis & Information: The risks related to genetic analyses can be to individuals or groups. These harms include stigmatization and impact insurability for life, disability, and long-term care insurance. If stored genetic information were re-connected to a participant's identity, personal information about the participant and the participant's health and risk of disease could become known to others. This could present unknown risks.

Risks Associated with Study Interventions and Run-in Activities

Acceptance Commitment Therapy (ACT): The ACT behavioral intervention includes discussing one's pain experience with a trained therapist and may make participants feel emotionally uncomfortable. These risks are minimal and are sometimes part of the therapeutic process. To reduce the disabling effects of depression, fear or other feelings, one may need to first recognize these before identifying healthy goals for improvement. Participants will meet with an assigned therapist four times and will be able to contact them at any time by email. The therapist will thoroughly explain treatment and what to expect. They will provide ongoing support over the course of treatment and, if applicable, will monitor the participant for worsening of depression or anxiety symptoms. Study participants may also reach out to study staff with any questions or concerns throughout the course of the study.

Duloxetine: Duloxetine will be administered with daily doses ranging from 30mg to 60mg. Participants will begin with 30 mg and may increase to 60 mg after seven days, if no or only mild side effects are experienced. Participants will be warned about the most common side effects with this drug, which include nausea, vomiting, nausea, dry mouth, constipation, diarrhea, fatigue, and difficulty sleeping. 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 is the increased risk of suicidality with initiation, especially in individuals under age 25. Participants on duloxetine (of all ages) will be monitored appropriately for clinical worsening, suicidality, or unusual changes in behavior. Participants reporting a history of bipolar disorder, manic episodes, or suicide attempts and participants who are currently breastfeeding will not be eligible for participation in the Duloxetine intervention.

Enhanced Self Care (ESC): The ESC intervention is an educational and self-care digital intervention. Risks are minimal.

Evidence-Based Exercise and Manual Therapy (EBEM): Manual therapy may be used to reduce pain and stiffness and improve range of motion, and exercises may be used to improve muscle strength, flexibility and endurance. Both are considered safe for the treatment of low-back pain, but side effects associated with spinal mobilization/manipulation and therapeutic exercise are common and benign. Approximately 50% of patients report local post-manipulation or exercise muscle and/or joint soreness which typically resolves within 24 hours. Participants may also receive soft-tissue mobilization, and risks associated with this procedure are considered to be mild. Mild muscle soreness at the site of soft-tissue treatment during and after treatment has been reported. Skin irritation has also been reported when massage lotions and oils were used. Exacerbation of any low-back problem is a common risk due to natural history of the condition. Education interventions may ask patients to discuss their pain experiences and the impact of their low back pain on various aspects of his or her life possibly resulting in emotional distress. EBEM is contraindicated for certain participants with uncontrolled high blood pressure or heart conditions**.**

Run-in: The Run-in period is comprised of informational materials delivered digitally. Risks are minimal.

Risks Associated with Confidential Information Disclosure

Despite significant protections being put in place to protect confidential participant information (e.g., protected health information (PHI)), breaches of confidentiality, while very unlikely, are possible. An example breach of confidentiality is the disclosure of a participant's protected health information to a party that is not approved to have access to that information. A breach of confidentiality will be considered as an unanticipated problem and, as such, will be reported to the IRB of record within 48 hours of the occurrence, and a remediation plan will be put in place immediately.

5.2.2. KNOWN POTENTIAL BENEFITS

The components of each study intervention have been independently shown to clinically improve pain intensity[10,14,18,24-28] and may improve other outcomes such as function or pain interference; however, neither improvement nor direct benefit is guaranteed to study participants. Study participants who improve on the treatment to which they are randomized will be allowed to continue that treatment either as a single treatment or augmented with an additional treatment. Participants who do not improve on the treatment to which they are randomized will be randomized to a new treatment. All study treatments will be provided free of charge to participants. Participants may also benefit by gaining new knowledge about their pain condition or by learning new pain self-management techniques. Participants may experience psychological benefit from interacting with study staff and personnel. Participation in the study may be beneficial to participants' general health, as participants might initiate and maintain healthy habits such as exercise. These benefits, if incurred, may be both immediate and long-term.

This research has the potential to benefit society in general by improving treatment for chronic low-back pain. Chronic low-back pain is a major cause of disability in the United States and causes both physical and emotional suffering. Patients are often unable to find adequate treatment for their condition, given the heterogeneity of patient phenotype including biomarkers, pain etiology and mechanism, and psychosocial characteristics. The goal of the study is to apply a precision medicine approach to chronic low-back pain treatment, which will allow more patients to receive the treatment that is likely to be best

for them. If providers are better able to target treatments, patients are likelier to improve. Long-term, this could reduce the prevalence of chronic low-back pain, improve pain and functional status, reduce the duration of symptoms, and reduce long-term opioid use.

5.2.3. ASSESSMENT AND MITIGATION OF POTENTIAL RISKS

Participant Understanding of Risks and Informed Consent

All participants enrolled in this study will provide informed consent based on an informed consent document that has been approved by the IRB of record for the study. The informed consent process will be administered by trained study staff and will include both verbal and written explanation of the study. This explanation will include describing the purpose of the study, phenotyping methods to be used, the time commitment required, all inclusion/exclusion criteria, potential risks and benefits, monetary and non-monetary compensation, study personnel contact information, and information on how study data and biospecimens will be shared within the BACPAC Consortium and with NIH approved repositories. All participants will be allowed to ask questions on any aspect of the protocol, and study personnel will provide answers and confirm there is no residual uncertainty regarding the study procedures prior to obtaining informed consent from the participant.

General Risk Mitigation Procedures

Protection of subjects from risk is multifaceted and includes monitoring the safety of the research participants, putting in place processes for minimizing research-associated risk, maintaining confidentiality of study data and participant identification, and reviewing and reporting adverse and unanticipated events.

Study staff at each site will be trained in HIPAA, CITI, and other human subjects research standards as required by site's institutional requirements. The Data Integration, Algorithm Development and Operations Management Center (DAC) will hold central training on study procedures and systems for clinical personnel prior to the start of the study and record these sessions for use by new staff members as needed during the study. If new procedures or forms are adopted during the study, additional training will be conducted via webinars. New clinical center staff will be trained by experienced staff at their site and through the training modules available via webinars. Each clinical site staff member will be certified on study procedures and systems, and certification records will be maintained at the sites for auditing. Each intervention arm will be delivered by appropriately trained and licensed personnel.

The measures taken to minimize risk associated with phenotypic assessments and study interventions are described below.

Risk Assessment & Mitigation for Phenotypic Assessments

Participants will be screened for contraindications to any of the BEST phenotyping procedures prior to enrolling in the study. All phenotyping activities (e.g., quantitative sensory testing, biomechanical assessments, blood draws) will be performed by appropriately trained and, where applicable, licensed personnel). Participating sites will be staffed by researchers with expertise in the assessment and treatment of chronic low-back pain, and the DAC will be responsible for ensuring all staff are trained and certified as required by the protocol prior to study launch.

Questionnaires: To minimize patient burden associated with completing a large number of questionnaires, as much as is feasible without sacrificing the validity of the data, participants will be

allowed to complete most questionnaires online prior to a scheduled visit or phone call assessment. This will allow participants to complete the questionnaires at their home or location of choice and to break up completion of the questionnaires into multiple sessions at their discretion. Participants will be instructed that they can contact study staff if at any point they become distressed while completing a questionnaire due to a lack of clarity about one or more questions or general discomfort caused by responding. While the completion of questionnaires will be incentivized, all participants will be told that they have the option to terminate participation without penalty and/or will be assisted in arranging medical/psychiatric help, if necessary.

Blood Draw / Venipuncture: In order to minimize risk of infection, venipuncture will be performed by trained medical personnel using aseptic technique including handwashing before and after the procedure and the utilization of sterile kits and gloves. Alcohol will be swabbed over the region of venipuncture prior to the procedure and a sterile bandage will be applied following the procedure.

Stool collection: Instructions regarding the safe collection of stool will be provided with each stool collection kit.

Biomechanical Assessment: Biomechanical assessments will be supervised by trained staff. Participants will be instructed that they can contact study staff if at any point they become distressed while completing an assessment.

Imaging: The primary established hazard associated with MR imaging is that the magnet exerts a strong force on metal objects. For this reason, metal objects are excluded from the vicinity of the magnet so that they will not become projectiles. In addition, each subject undergoes a standard screening procedure to determine whether they have any implanted materials that may pose a risk. If there is any doubt about the nature of any implanted material, the subject will not be scanned. Participants will be instructed to bring or wear clothing without metal fasteners and remove jewelry and any other metal objects from their body. 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. MRI sessions will be conducted by trained personnel. Participants 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 peripheral nerve stimulation is low. Participants who report pregnancy will be excluded from MRI portion of the protocol.

Quantitative Sensory Testing (QST): Study personnel will be trained by the investigators to be sensitive to participant discomfort and concerns. Participants will be instructed that they can stop any QST procedure anytime that the pain or unpleasantness of the task becomes unbearable. All procedures have been thoroughly evaluated for reliability and safety, and are well tolerated by individuals with chronic pain, causing no more than temporary mild discomfort in the body regions that will be evaluated.

Genetic Analysis: Current federal law will help protect study participants from genetic discrimination in health insurance and employment.

Risk Assessment & Mitigation for Study Interventions

Participants will be screened for contraindications to any of the BEST study interventions prior to enrolling in the study. Participants who have a contraindication to a study intervention and who are

otherwise eligible for the study will be allowed to participate in the study but will not be randomized to the intervention for which they have a contraindication. In Sections 10.1 (Acceptance Commitment Therapy), 10.2 (Duloxetine), 10.3 (Enhanced Self Care), and 10.4 (Evidence-Based Exercise and Manual Therapy) specific details regarding risk assessment and mitigation are given for each study intervention.

Participants will be advised that they should contact study staff regarding any side effects or unexpected adverse events that occur while enrolled in the study. Prior to the start of a new study intervention, participants will be informed that if they are unable to tolerate the intervention, they are permitted to cease the intervention. Specifically for duloxetine, participants will be instructed on how to safely taper off the medication. In addition, study staff will conduct a phone call assessment with all participants approximately midway into each of the two intervention periods to evaluate pain-related outcomes as well as to ascertain how well the participant is tolerating their current study intervention(s). Participants who indicate they are unable to tolerate the intervention will be safely transitioned off their current intervention but, if in intervention period one, will be allowed to be randomized to a new intervention in the second study period. Additionally, all participants will be assessed for unexpected and adverse events 4 weeks after the end of the second intervention period (i.e., after completion of all study treatment).

Acceptance Commitment Therapy: Participants will interact with their therapist at least weekly, and the therapist will provide support as well as monitor for worsening of depression or anxiety symptoms including suicidal ideation. Participants will be encouraged to contact study staff with questions or concerns throughout the course of the study.

Duloxetine: Participants on duloxetine will be monitored appropriately for clinical worsening, suicidality, or unusual changes in behavior. Participants may be referred for appropriate treatment including emergency services if required. Participation can also be discontinued if there is active suicidal ideation.

Enhanced Self Care: The ESC intervention is an educational and self-care digital intervention. Risks are minimal; therefore, no intervention-specific risk mitigation is planned.

Evidence-Based Exercise and Manual Therapy: The EBEM intervention will be delivered by trained physical therapists or Doctors of Chiropractic. Participants who report local post-manipulation or exercise muscle and/or joint soreness will be instructed on appropriate self-care.

Run-in: The Run-in period is comprised of informational materials delivered digitally. Risks are minimal; therefore, no intervention-specific risk mitigation is planned.

Risk Assessment & Mitigation for Disclosure of Confidential Information

Several measures have been taken to minimize the risk of breach of confidentiality via unintended disclosure of confidential information. These include the general risk mitigation procedures described above (e.g., ensuring study staff have completed HIPAA, CITI, and other human subjects research training), providing highly secure electronic data collection systems and procedures (as described in Section 14), and collecting only essential identifiable information that is required for the study's scientific objectives and for critical operational reasons (e.g., contact information for scheduling study visits and conducting phone call assessments).

All reasonable steps will be taken to protect the privacy of participants. Each study participant will be assigned a unique study ID upon enrollment. All data and other artifacts collected for the study will be

identified by the participant's study ID. This includes data collected using the Carolina Data Acquisition and Reporting Tool (CDART) data management system, the online survey platforms, biospecimens, and web-based applications. Personally identifiable information will be segregated from other data. CDART implements a granular authorization model and enforces the principle of lease privilege access. Only a restricted set of authorized users will be allowed access to enter or view personal information. To further restrict data access, the CDART database is behind a network firewall which is open only to the CDART system itself.

The CDART data management system has robust security features including unique user logins with expiration dates and complex password requirements; storage of hashed passwords only; granular permissions based on user requirement to enforce the principle of least privilege access; and encrypted data transmission. The secure server environment where the systems that host CDART reside is located within a hardened data center on the UNC campus and is governed by standard UNC information security guidelines. Weekly vulnerability detection scans are performed using third-party vendor scanning tools, which include full administrative credentials to perform maximum detection techniques. Real-time virus protection software is implemented, and weekly full system virus scans are performed. Daily backups of the data are made and stored in an off-site location. CDART is 21 FDA Part 11 compliant.

5.2.4. RISK/BENEFIT JUSTIFICATION

The risks associated with phenotyping procedures are minimal. A greater understanding of the biomarkers, biomechanics, and etiology of chronic pain will improve future treatment recommendations and enhance quality of life for chronic low-back pain patients.

The risks associated with study procedures and interventions are generally minimal. The components of each of the study interventions have been previously studied and are in current clinical practice. There are well-studied side effects associated with duloxetine, but these side effects are generally mild to moderate for participants. Moreover, participants will be monitored for side effects and advised to discontinue if duloxetine is not well tolerated. These non-invasive treatments may reduce pain intensity, improve function, enhance self-management capacity, and increase psychological flexibility. Altogether, the potential benefit of these interventions outweighs the potential risk. The screening and monitoring of participants by study sites will ensure that risk remains low.

6. OBJECTIVES AND ENDPOINTS

The BEST Trial will inform a precision medicine approach to cLBP and is designed to identify treatments that are most effective in identifiable subgroups of patients. Therefore, the study was designed to estimate dynamic treatment regimes rather than to test the overall effectiveness of any single intervention or combination of interventions.

The primary objective is to estimate an algorithm to assign sequences of two cLBP treatments based on phenotypic markers and an individual patient's response to the initial treatment (*i.e.,* a dynamic treatment regime) that optimizes effectiveness.

In this trial, phenotypic markers will not be used to assign treatments, rather participants will be randomly assigned to treatment. Response to initial treatment will guide second-stage randomization and will be assessed with the Pain, Enjoyment of Life, and General Activity (PEG) scale and the Patient

Global Impression of Change (PGIC) 12 weeks after the first randomization. The primary analysis will then estimate an algorithm that can be applied to *cLBP* patients that will optimally assign treatments based on a patient's phenotypic markers and changing response (a dynamic treatment regime or DTR). Phenotypic markers that will be considered include, for example, preference for treatment and outcome priorities, history of depression, and time since diagnosis of chronic back pain. Study participant phenotypic markers will be assessed at baseline and a subset will be measured at the end of the first intervention period. As part of this analysis, we will compare the estimated best DTR that does *not* use phenotypic variables or participant response with the estimated *optimal* DTR A hypothetical example of a DTR that we might estimate would involve a sequence of two decision rules: Individuals with chronic low-back pain receive physical therapy for 12 weeks and if pain intensity and interference are below a given threshold, continue regular follow up with patient; if pain interference is over the threshold, provide patient with prescription for duloxetine for 12 weeks.

This procedure will be applied to the following primary and secondary endpoints:

- **Primary endpoint: 24-week change from baseline in patient-reported pain intensity and interference**, measured with the Pain, Enjoyment of Life, and General Activity (PEG) scale at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in pain interference**, measured with the 4-item PROMIS Pain Interference scale (PROMIS-PI, 4a) at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **Incidence of opioid use,** measured by self-report at Visit 2 (24 weeks of treatment)
- **24-week change from baseline in physical function**, measured with the PROMIS-PF Short Form 6b at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in depression score**, measured with the PROMIS 4-item depression scale from the PROMIS 29 profile at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in anxiety score**, measured with the PROMIS Emotional Distress-Anxiety scale (PROMIS-EDA 4a) at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in sleep disturbance,** measured with the PROMIS short form 6a at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in sleep duration,** measured at Visits 0 (baseline) and 2 (24 weeks of treatment)

The PEG is a 3-item assessment of pain intensity and interference with enjoyment of life and general activity over the past week. This scale is validated, has low participant burden, is responsive to change, and captures multiple core outcome domains recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) and that are valued by people who experience chronic pain.[29-31] In addition, pain intensity was considered the primary outcome of interest by the BACPAC Patient Advisory Board. Pain interference with be assessed using PROMIS-PI, which has demonstrated reliability and validity across diverse populations for the assessment of the degree to which pain interferes with physical, mental, and social activities.[32-34] Self-reported opioid use is included as a secondary endpoint. Additional secondary endpoints of physical function, depression, anxiety, and sleep disturbance are patient-centered and will be assessed using validated instruments from the PROMIS measure set. Depression and anxiety, common among individuals who experience chronic pain, negatively affect quality of life.[35] Finally, PGIC is of key importance in the determination of response to treatment following the first randomization because it is valued by patients, integrates both positive and negative factors about treatment, and is responsive to change under pharmacologic and

nonpharmacologic treatment. It has been well validated,[36,37] is reliable and is recommended as a global outcome measure for chronic pain by the IMMPACT.

The study has the following 3 secondary objectives:

Estimate DTRs that optimally balance multiple outcomes, taking into account participant preferences for outcomes including pain intensity, pain interference, physical function, opioid use, depression, anxiety, sleep duration and sleep disturbance.

Identification of DTRs that appropriately balance multiple outcomes will be accomplished by collecting participant preferences for outcomes at the two randomization points (Visit 0 and Visit 1) as well as overall satisfaction of the treatment at 12 and 24 weeks. This participant preference information will not be used to assign treatment during the study but will be used to estimate a participant-preference based DTR. The participant preference tool, CAPER, has been designed for use in this study and will be validated as part of its ongoing development in a BACPAC ancillary study.

Estimate DTRs that incorporate additional phenotypic markers (i.e., deep phenotyping) collected on a sub-set of participants.

A subset of participants (~n=200) will undergo 'deep' phenotyping that will include more comprehensive biomechanical assessments, functional brain imaging, and qualitative sensory testing. We will apply procedures discussed for the primary objective to estimate and identify DTRs to evaluate in future studies. While the precision of these estimates will be lower given the reduced sample size, we will learn what additional phenotypic measures may predict differential response to treatment.

Assess whether effectiveness is sustained on outcomes collected 24 weeks after randomization to the second treatment.

Endpoints will be the same as listed for the primary objective except that they will be measured at the final study visit (Visit 3) occurring 24 weeks after the second-stage randomization. Assessment of this aim will utilize procedures discussed for the primary objective.

The study has the following 3 exploratory objectives:

Evaluate the comparative effectiveness of individual treatments.
Evaluate the comparative effectiveness of different treatment regimes (i.e., a particular regime with a given set of rules at each decision point).
Evaluate the impact of treatment order on outcomes.

For these analyses we will estimate average treatment effects. Endpoints will include the primary and secondary endpoints identified in the primary objective, measured at 12 and 24 weeks after the first randomization.

7. STUDY DESIGN

7.1. OVERALL DESIGN

This study is a multi-site, sequential, multiple assignment randomized trial (SMART) to estimate DTRs based on four evidence-based interventions for chronic low-back pain. The trial is designed to meet the primary objective of estimating an algorithm for optimally assigning treatments based on an individual patient's phenotypic markers and response to treatment. Interventions being evaluated in this trial are: (1) enhanced self-care (ESC), (2) acceptance and commitment therapy (ACT), (3) duloxetine, and (4) evidence-based exercise and manual therapy (EBEM).

Each participant will complete an initial screening call and enrollment visit, followed by a 2-week run-in period, post run-in eligibility screening, two consecutive 12-week treatment periods, and a minimum of 4 weeks of follow-up. Participants will be screened using a combination of telephone assessments prior to, and in-person evaluation during, an initial screening period. Eligible participants who provide consent to participate will be enrolled and enter a 2-week run-in period focused on patient engagement. The goals of the run-in are to engage individuals from diverse backgrounds, educate potential participants about the study, assess adherence and engagement prior to randomization, enhance retention, and establish communication between participants and members of the study team. In the first treatment period, participants will be randomly assigned at Visit 0 to one of the four study interventions. For the second treatment period, depending on response to their initial treatment, participants will be assigned to: (1) maintain their current intervention, (2) augment their current intervention with another study intervention, or (3) switch to a new study intervention. For treatment actions (2) and (3), the additional or new intervention will be randomly determined independent of participant response to the initial treatment. Patient Reported Outcome (PRO) assessments will be performed at baseline (Visit 0/Week 0) and at Weeks 6, 12, 18, 24, and 36, and phenotyping will be performed at baseline (Visit 0/Week 0) and at Weeks 12 and 24 (Visits 1 and 2)

At the end of the run-in period, participants will be re-assessed for eligibility. Those meeting requirements for randomization (Section 8) will be randomized to one of the 4 first line treatments. At the baseline visit (Visit 0), all participants will undergo baseline data collection and phenotyping. Data collected for phenotyping will include patient-reported outcomes, spinal imaging, biomechanical assessments, and collection of blood and stool. As described in Section 5.2.2, some of these data will be collected at home prior to the in-person portion of the study visit. A subset of eligible and willing participants (~n=200) will undergo additional phenotyping. Details of the phenotyping assessments are available in Section 9. A subset of phenotypic markers will be re-assessed Week 12 (Visit 1) and Week 24 (Visit 2).

Participants will be assessed for response to treatment Week 12 (Visit 1) and Week 24 (Visit 2) using the PGIC and PEG. Participants will be grouped into one of four responder classes using the PGIC and PEG (see Section 7.1) and assigned to the following based on their responses:

- maintain current treatment (PGIC=1-2, PEG <4),
- augment the current treatment with a randomly selected additional treatment (PGIC=1-2, PEG ≥4),
- be randomized to augmentation or switching to a new treatment (PGIC=3-4), or
- switch to a randomly selected new treatment (PGIC=5-7)

Since the ESC modules focus on self-care, education and a walking program, requiring participants in this intervention arm to cease these activities is not practical; therefore, individuals assigned to ESC at the first randomization will maintain ESC if PGIC is 1-2 and PEG<4 else they will augment ESC with a randomly selected additional treatment. Participants who wish to discontinue treatment but whose

PGIC is less than 6 and who are not contraindicated to their current treatment will be asked to continue first-line treatment until the end of the 12-week treatment period.

All participants will also receive an assessment 4 weeks after the end of the second treatment period for safety purposes (week 28). Participants, whose randomization to the first intervention is at least 36 weeks prior to the end of data collection, will be assessed for outcomes at 36 weeks.

Participants may need to discontinue treatments prior to the end of the 12-week treatment period (e.g., following an adverse reaction to duloxetine; see Section 10.2.1 for list of reasons). Participants needing to discontinue first period treatment will be switched to a randomly selected second treatment at Visit 1. Participants needing to discontinue second period treatment will remain in the study and undergo all future assessments for which they are eligible.

The study will enroll approximately 820 participants in order to randomize approximately 740 individuals and to have approximately 630 completers (i.e., 15% dropout rate after randomization assumed). Assuming dropout occurs uniformly across study interventions, the sample size of 740 randomized will result in having approximately 80% probability of estimating a DTR within 90% of the optimal DTR based on the study's primary endpoint. See Section 13.2 for additional details on sample size needs for precision medicine objectives, including assumptions regarding intervention effect sizes.

The interventions under evaluation are evidence-based, with established efficacy and are standard of care. Therefore, we do not expect they will pose safety risks such that these interventions need to be stopped before the end of the study. Safety data and adverse events will be monitored. These data will be reported to and reviewed by a Data Safety and Monitoring Board. Generally, this trial will inform a precision medicine approach to the treatment of chronic low-back pain and therefore we are not planning interim analyses for futility or efficacy in order to maintain sufficient power for the precision medicine analyses. Blinding is not feasible for study participants or staff involved in the delivery of interventions. Investigators involved in the analysis of study data will be blinded to treatment assignment.

The study timeline involves approximately 9 months of participant enrollment across 12 sites for a total of 820 enrolled. Sites will enroll ~7 participants per month. We anticipate that ~90% of participants who consent at the Enrollment Visit will be randomized at the end of the 2-week run-in at Visit 0 and that 85% of randomized participants will complete all study activities. The total study duration for all participants is 38 weeks.To minimize participant burden, where possible, data will be collected remotely.

7.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN

As described above, this trial will inform a precision medicine approach to the treatment of cLBP. This goal is motivated by the observation that, while numerous treatments exist for cLBP, all are associated with relatively small population average treatment effect sizes. This study seeks to understand how to better match future patients to the most appropriate treatment based on their phenotypic measures to optimize outcomes. To achieve this goal, we have chosen to conduct a sequential, multiple assignment, randomized trial (SMART).

7.3. JUSTIFICATION FOR DOSE/INTERVENTION REGIMENS

The justifications for doses for individual treatments are found in Sections 10.

7.4. END OF STUDY DEFINITION

For study non-completers, the end of the study will coincide with the point in time when the participant notifies study personnel that they wish to discontinue the study. If the reason for study discontinuation is related to an incidence adverse event, and if the participant consents to further contact by study staff, the participant will be contacted by phone 4 weeks after completion of the study discontinuation visit to follow up on adverse events and document their resolution or status.

The study will end approximately 38 weeks after randomization (at the time of completion of the 12-week post-intervention follow-up period).

8. STUDY POPULATION

8.1. STUDY INCLUSION CRITERIA

To be eligible, an individual must meet all of the following inclusion criteria:

- Ability to read and understand English
- Provision of signed and dated informed consent form(s)
- Willing and able to receive study-related messages and survey links via email
- Willing and able to receive study-related phone calls
- Age 18 years old or older
- Low-back pain for at least 3 months and occurring on at least half the days in the past 6 months
- Contraindicated to no more than one of the study interventions at the time of eligibility assessment(s)
- Eligible to receive at least three of the four study interventions and willing to receive any intervention for which they are eligible
- A PEG score 4 or higher prior to the Run-in period
- Willing and able to undergo required phenotyping as defined in Section 9
- Regular reliable access to an internet-enabled device such as a smart phone, tablet, or laptop computer
- Meet Run-in period engagement eligibility criteria:
    - Completion of two Run-in study information modules prior to period 1 randomization (Visit 0)
- Low-back pain more severe than pain in other parts of the body
- Available to complete the full study protocol (approximately 9 months)

8.2. STUDY EXCLUSION CRITERIA

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

- Pregnant at the time of Visit 0 (Baseline)
- Affirmative participant response to any of the following conditions:
    - Progressive neurodegenerative disease
    - 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)
- Diagnosis of any vertebral fracture in the last 6 months
- Osteoporosis requiring pharmacologic treatment other than vitamin D, calcium supplements, or bisphosphonates.
- History of any bone-related cancer or cancer that metastasized to the bone
- Currently in treatment for any non-skin cancer or plan to start non-skin cancer treatment in the next 12 months
- History of any non-skin cancer treatment in the last 24 months
- Visual or hearing difficulties that would preclude participation
- Uncontrolled drug/alcohol addiction
- Individuals actively pursuing disability or workers compensation or involved in active personal injury-related litigation
- Currently participating in another interventional pain study

- Any condition that, in the opinion of the investigator, would preclude the patient from being able to safely participate in in the trial

8.3. STUDY INTERVENTION CONTRAINDICATIONS

ACT intervention contraindications
An individual who meets any of the following criteria will be excluded from being randomized to receive ACT during the study:

- Currently receiving or intending to receive within the next few months any pain-specific psychotherapy, e.g., Cognitive Behavioral Therapy, directed towards pain even if it is only a part of the treatment, and delivered by a psychologist or social worker

Duloxetine intervention contraindications
An individual who meets any of the following criteria will be excluded from being randomized to receive duloxetine during the study:

- Pregnant: If the participant becomes pregnant during the study, duloxetine will be rapidly tapered.
- Currently taking any of the following:
  Duloxetine
  Lithium
  Tramadol (Ultram, Ultracet)
  St. John's Wort
  Prochlorperazine (Compazine)
  Thioridazine (a psychiatric medication)
  Propafenone or Flecainide (for heart rhythm problems)
  Ciprofloxacin (Cipro, an antibiotic)
  Linezolid (Zyvox, an antibiotic)
  Methylene Blue
  Cimetidine (Tagamet, for heartburn)
  Bupropion (Wellbutrin)

SNRIs:
- Venlafaxine
- Milnacipran
- Duloxetine
- Sibutramine
- Atomoxetine
- Desvenlafaxine
- Levomilnacipran

SSRIs:
- Sertraline
- Paroxetine
- fluoxetine
- escitalopram
- citalopram
- fluvoxamine
- Vortioxetine (Trintellix)

Any other contraindicated SNRIs, SSRIs, and antidepressants

- Reporting a current or previous diagnosis of any of the following
  - Renal dysfunction
  - End-Stage Renal Failure
  - Hepatic dysfunction
- Previous allergic or other severe adverse reaction to duloxetine or, as determined by the site PI, a medicine with duloxetine cross-reactivity.
- History of bipolar disorder, manic episodes, or suicide attempts
- Currently breastfeeding

EBEM intervention contraindications
An individual who meets any of the following criteria will be excluded from being randomized to receive EBEM during the study:

- Currently receiving or intending to receive within the next few months any type of manual therapy or exercise treatment for low-back pain from a licensed provider
- Uncontrolled high blood pressure (≥150 systolic and/or ≥100 diastolic)
- Uncontrolled coronary artery disease
- Inability to walk at least 50 feet unassisted
- Contraindication for manual therapy
- Contraindication for participation in an exercise program

ESC intervention contraindications
An individual who becomes pregnant during the study will be counseled to stop NSAIDs.

8.4. PHENOTYPING CONTRAINDICATIONS

Blood Draw / Venipuncture:

- Active infection over the site of blood draw
- Recent or recurrent history of fainting/vasovagal syncope with previous blood draws
- Lack of vascular access (inability to find venous access)

Stool collection:

- None

Biomechanical Assessment:

- Inability to walk at least 50 feet unassisted
- Inability to stand for at least 10 minutes
- Participants with an allergy to adhesives will not have adhesive sensors placed on their body

Imaging:

- Certain implanted medical devices (e.g., implanted cardiac devices, cochlear implants, or intracranial aneurism clips)
- Ferrous metal (e.g., wire mesh, screws) in the body that will cause safety issues (titanium implants are acceptable)[38]
- Waist circumference equal to or greater than the bore diameter of the study site scanner
- Pregnancy

QST:

- Peripheral neuropathy
- Participants with a history of Raynaud's Syndrome will not undergo cold-water immersion
- Participants with circulatory or sensory problem in the hands will not undergo cold-water immersion
- Participants with SBP ≥150 and/or DBP ≥100 will not undergo cold-water immersion

8.5. LIFESTYLE CONSIDERATIONS

Not applicable

8.6. SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

8.7. STRATEGIES FOR RECRUITMENT AND RETENTION

Study participants will be recruited from direct contact in clinical settings, screening via electronic health records (EHR) for chronic back pain, online surveys, and through community outreach. Sites may also choose to compensate current participants who refer others with cLBP that enroll and remain in the study. Site coordinators will generate a programmable phenotype based on the inclusion/exclusion criteria to generate a list of medical record numbers/unique patients to be screened. Site coordinators will use electronic health records (EHR) to search for ICD10 codes indicating the presence of chronic low back pain M54.40, M54.41, M54.42, M54.5, and M54.89 within the past 1 year in order to generate a list of medical record numbers/unique potential participants. Progress notes housed within the EHRs may also be searched by an algorithm for the presence of "low back pain," "back pain," or "lumbago" in order to generate a list of medical record numbers/unique potential participants. Site coordinators may use additional ICD10 codes and progress note keywords as they develop and identify effective search

parameters. The list of unique potential participants will be updated as frequently as daily such that new patients coming into the system with chronic low back pain or who develop chronic low back pain may be screened for eligibility. Patient's records will be further screened to determine if any exclusion criteria are met. Patients meeting the inclusion/exclusion criteria will be contacted via phone for the initial pre-screening call, sent a letter assessing interest in the study, or approached during a scheduled clinic visit as allowed by the site's regulatory guidelines.

Enrollment of a diverse sample will be monitored in real time to ensure overall enrollment approximates the US population experiencing low-back pain. The DAC will assess subgroup enrollment targets each month and instruct sites to adjust recruitment to correct under or overrepresentation of any particular subgroup.

Various approaches will be considered to enhance participant retention including scheduling flexibility, phone calls from the coordinators (or electronic messaging), updates on study progress (such as regular study newsletter targeted at the participants, celebrating milestones), and invitation to provide input into future studies.

Recruitment and retention throughout the study will be monitored by the DAC, which will oversee development of materials to facilitate recruitment and retention, monitor progress of both as the study progresses, and develop strategies for addressing recruitment and retention issues as they arise. The Data Safety and Monitoring Board (DSMB) will monitor accrual at each clinical center based on periodic summary reports provided by the DAC for their review (see Section 14.1.8) and make recommendations on proposals to address recruitment or retention challenges, such as adding clinical centers, if needed.

9. PHENOTYPIC ASSESSMENTS

Phenotypic assessments will take place during the study. Some assessments will be required in order for inclusion in the study, therefore, individuals who are contraindicated to any of the required phenotypic assessments will not be eligible for study participation. All participants in the study will be required to answer questionnaires, receive a physical assessment, receive a motion assessment lasting approximately 10 minutes at each of 3 separate visits, provide blood samples at each of 3 separate visits, receive an at-home stool collection kit to provide a single stool sample, and receive 1 spine MRI lasting approximately 30 minutes. Total patient time for *required* phenotyping assessments is approximately 3 to 5 hours at the baseline visit and approximately 1 hour at the 12- and 24-week visits.

Additional assessments are not required to participate in the trial. It is expected that approximately one third of enrolled participants will opt to undergo these additional assessments. This subset of participants will, in addition to the required assessments, receive motion assessments lasting approximately 40 minutes at each of 3 separate visits, be asked to wear an actigraphy sensor at home continuously for 7 days, receive an advanced spine MRI lasting approximately 30 minutes, receive a brain MRI lasting approximately 60 minutes at each of 3 separate visits, and receive Quantitative Sensory Testing lasting approximately 60 minutes at each of 3 separate visits. Total patient time for *additional* phenotyping is approximately 4 hours and 40 minutes at the baseline visit, and approximately 3 hours and 40 minutes at the 12- and 24-week visits.

Required Phenotypic Assessments	**Optional Additional Phenotypic Assessments**
20-minure motion assessment at 3 time points	60-minute motion assessment at 3 time points
60-minute basic spine MRI at 1 time point	7-day continuous at-home activity monitoring via a wearable sensor
Questionnaires/PROs	30-minute advanced spine MRI at 1 time point
Blood draw at 3 time points	60-minute brain MRI at 3 time points
Provision of stool sample at 1 time point	Quantitative Sensory Testing at 3 time points

9.1. QUESTIONNAIRES

Questionnaires pertaining to pain, medication use, and history of chronic low-back pain and other pertinent comorbidities will be delivered as part of the study. A complete list is included in Section 16.

9.2. BLOOD DRAW / VENIPUNCTURE

All participants will undergo the following blood draws at Baseline (Visit 0) and the 12- and 24-week visits (Visits 1 and 2), with the exception of the PAXgene DNA tube which will be collected only at the Baseline visit. At each visit, approximately 32mL of blood will be drawn and collected in the following tubes:

- 1 TruCulture tube
- 1 Sodium Heparin tube
- 1 EDTA tube
- 1 PAXgene DNA tube
- 3 PAXgene RNA tubes

Blood samples will be minimally processed per protocol at the study site and stored until such time as they are shipped to the NYU Langone Health Center for Biospecimen Research and Development (CBRD). Batch sample shipments will occur at a frequency specified by the DAC.

During the study period, Cytokines/MMP, TruCulture, and Genome-wide association study (GWAS) analyses will be conducted on the study samples. Blood samples collected in the Sodium Heparin tube and PAXgene RNA tubes will be stored for possible future analyses.

At the end of the study, the CBRD will ship all remaining samples to the repository(ies) approved by NIH.

9.3. STOOL COLLECTION

Study sites will provide participants with stool collection kits to be used at home. A pre-paid shipping label will be provided with each kit. Participants will be instructed to return their stool sample to the CBRD where the sample will be stored for possible future analyses.

At the end of the study, the CBRD will ship all remaining samples to the repository(ies) approved by NIH.

9.4. BIOMECHANICAL ASSESSMENT

All participants will undergo a single biomechanical assessment at Baseline (Visit 0) and the 12- and 24-week visits (Visits 1 and 2). At each visit, sensors will be placed on the participant's pelvis and chest, and the participant will be asked to complete a series of motions. Data from these motions will be uploaded from the sensors to the cloud. This biomechanical assessment requires approximately 10 minutes of patient time.

Study participants who participate in the additional phenotypic assessments will undergo three additional biomechanical assessments at Baseline (Visit 0) and the 12- and 24-week visits (Visits 1 and 2). These additional assessments require proprietary sensors be placed on the skin of the participants' back, waist, and/or hip using adhesive tape, and the participant will be asked to complete a short series of motions that include several repetitions of bending, side bending, and twisting as far as remains comfortable. Participants will also be asked to complete a series of repeated sit-to-stand maneuvers. Manual palpation of the participant's spine may be used to ensure correct placement of the sensors. Additionally, some of these same motions will be performed in front of a 3D depth camera. Data from these motions will be uploaded from these sensors to a secure location on the cloud before being securely transferred to the BACPAC Data Portal under the guidelines outlined in the BACPAC Data Portal Transfer Standard Operating Procedures (SOP). The complete set of these additional biomechanical assessments will require approximately 50 to 60 minutes of patient time.

Study participants who participate in the additional phenotypic assessments will also be provided with actigraphy sensors to be worn continuously for 7 days at home. At the end of the 7-day assessment, participants will return the sensor to the clinic using the pre-paid label provided. Data from the sensors will be uploaded to a secure location.

9.5. IMAGING

All participants will undergo a single MRI of their lumbar spine at Baseline (Visit 0). This scan requires approximately 30 minutes of patient time. The following pulse sequences are required:

- Sagittal T2-weighted with fatsat (SAG T2 fs)
- Sagittal T1-weighted without fatsat (SAG T1)
- Axial T2-weighted without fatsat (AX T2)
- Axial T1-weighted without fatsat (AX T1)
- Coronal T1-weighted without fatsat covering both SI joints (COR T1)
- Sagittal T1-weighted without fatsat for SI joints (SAG T1)

Study participants who participate in the additional phenotypic assessments may undergo an advanced MRI scan of their spine at Baseline (Visit 0). This scan requires approximately 30 minutes of patient time in addition to the required scan, for a total of approximately 60 minutes of patient time. The following pulse sequences will be collected on as many participants as is possible given individual site technology:

- MR spectroscopy

Study participants who participate in the additional phenotypic assessments will undergo an MRI of their brain at Baseline (Visit 0) and the 12- and 24-week visits (Visits 1 and 2). This scan requires approximately 60 minutes of patient time. The following scans are required:

- Tri-Planar Scout
- 3D MP-RAGE
- Resting State
- Diffusion Tensor Imaging

Imaging Data

DICOM images will be transferred to the BACPAC Data Portal to allow radiologists or others to analyze centrally. Personally identifiable information will be removed from all images prior to uploading the

image to XNAT. Stored images will contain only the participant ID, the date of the image, and the scan type.

Spine MRIs will be transmitted securely from the BACPAC Data Portal to a central reading center where they will be processed for tissue segmentation and measurement prior to the DICOM images being transmitted back to the BACPAC Data Portal.

Advanced Spine MRIs (i.e., MR spectroscopy acquisitions) will be transmitted securely from the UNC secure OneDrive to a commercial entity where they will be processed. The resulting reports will then be transmitted back to the UNC secure OneDrive.

Scanning a test subject prior to implementing imaging protocols is optional. Sites choosing to scan a test subject must meet their local IRB requirements. Test subject data will not be included as part of trial data.

9.6. QUANTITATIVE SENSORY TESTING

Study participants who participate in the additional phenotypic assessments will undergo quantitative sensory testing, which is comprised of the three components below. QST requires approximately 60 minutes of patient time.

Pressure pain sensitivity

Pressure pain sensitivity will be assessed using an analog algometer with a 1-cm^2 rubber probe (FPK25, Wagner Instruments, Greenwich, CT, USA) to quantify pressure pain thresholds (PPT). The primary test site will be located in the lumbar region by the participant's response to manual over-pressure (springing palpation) performed in the prone position. The control site will be located over the contralateral trapezius muscle (diagonal from lumbar site). Pressure will be manually increased at a rate of rise of 0.5 $kgf/cm^2/s$ (10 kg max, metronome guided) until participants first report that the pressure sensation becomes painful. Pressure intensity (in kgf/cm^2) read from the algometer at that time is considered the PPT. Measurements will be conducted 3x/site with 60-s rest intervals between each pressure application. Probe placement will be varied slightly trial to trial to prevent sensitization from repeated testing of the same site. Mean PPT will be used for analysis.

Temporal Summation

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.[39-41] Enhanced temporal summation is common in chronic pain and is predictive of pain outcomes.[43,44] We will evaluate temporal summation using a 40g Neuropen Neurotip (Owen Mumford, Oxfordshire, United Kingdom) applied to the skin of volar forearm and lumbar region, following a train of 10 identical stimuli (1 Hz) using a metronome for timing. Participants will report retrospectively the pain intensity of the 1st and 10th pinprick using a 0-10 numerical rating scale (NRS; 0 = no pain, 10 = worst imaginable pain). The palmer forearm and lumbar region will each be tested three times. Temporal summation for each site will be calculated as the mean difference in pain ratings of the 1st and

10th stimulus. Participants will also rate any ongoing *pain aftersensations* at 15- and 30-s following each train of stimuli.

Conditioned Pain Modulation

Immersion of one hand (ipsilateral to the primary lumbar pain site) into a circulating cold-water bath (10°C; NESLAB Digital One RTE 7, Thermo Scientific, Newington, NH, USA, or similar) will serve as the conditioning-stimulus and PPT at the contralateral trapezius will serve as the test-stimulus. This method is consistent with that of Locke[45]and others.[46,47] Baseline measurement 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 approximately 10 cm above the wrist into the water bath. The hand will be immersed for 60-s; perceived pain of the water will be rated at 30-s after hand immersion, and at 60-s after hand immersion, or immediately at hand withdrawal, using a 0-10 NRS to determine the adequacy of conditioning pain.[48] Trapezius PPT will re-measured 3x after the hand is withdrawn from the cold water. 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.

10. STUDY INTERVENTIONS

10.1. STUDY INTERVENTION(S) ADMINISTRATION: ACCEPTANCE COMMITMENT THERAPY

10.1.1. STUDY INTERVENTION DESCRIPTION

ACT is a process-based therapy that is among the third-wave cognitive behavioral therapies. It is well established for the treatment of chronic pain.[7-12] The goal of ACT is to build psychological flexibility thereby interrupting pain avoidance behavior patterns. Instead of targeting symptom reduction, ACT seeks to help individuals produce more successful responses to symptoms that are aligned with their values and goals. The 6 core therapeutic processes are acceptance (embracing unwanted experiences), cognitive diffusion (differentiating between thoughts and experience), present-focused attention, self-as-context (distinguishing between observations and the observer), values, and committed action (choosing action based on values). These processes are summarized as 'open, aware and engaged' behavior.[49] Treatment methods are experiential, including mindfulness exercises, metaphor, and identification of values. ACT can be delivered in person as well as over the internet. Internet delivery of ACT has been demonstrated to be similarly effective as in-person. It is also well-suited for pain patients with mobility issues, for individuals residing in rural areas or without transportation, and for areas without local qualified providers of ACT.[11,49-51,]

Participants randomized to ACT will take part in 12 sessions over the course of a 12-week treatment period (Section 10.1.2). There will be a combination of 4 remote face-to-face visits with a therapist and 8 therapist-supported online sessions (self-directed online modules plus provider coaching via an online messaging system). Qualifying therapists will include psychologists or social workers with training in chronic pain management and experience delivering ACT. Section 10.1.2 describes each session, delivery mode, approximate timing over the course of 12 weeks. Session content is based on ACT interventions found to be effective for chronic pain that have been adapted for online delivery.[12,52,53]

During the initial session, the therapist will establish rapport, discuss goals of treatment, review the online protocol, conduct a brief assessment, and describe the treatment in detail. During subsequent face-to-face sessions with the therapist, participants will be encouraged to share their experience of skills practice and mastery, provide examples of skill use at home, and describe what barriers they encountered. Online sessions will deliver the ACT content that focuses on helping participants accept pain, connect with negative thoughts and emotions, develop mindfulness and identify and commit to values and goals that are important to them. The online modules will consist of a combination of text, audio and video content. In-session exercises are intended to build psychological flexibility and skills in the 6 core therapeutic processes (acceptance, cognitive diffusion, present-focused attention, self-as-context, values, and committed action). After each online session, participant responses are sent to the therapist who will provide feedback by way of an online messaging system. All remote face-to-face therapy visits will take place virtually via a HIPAA-compliant platform such as Zoom. Access to the online content will require log-in via a personal account established at Visit 0.

Participants are encouraged to practice skills at home daily, repeating exercises from that week's session (as well as those from previous weeks) and to record their progress in a daily diary. Participants provide feedback by way of brief questionnaires before and after each session and responses are sent to therapists as part of the digital platform. The platform includes an internal messaging service that allows for provider coaching throughout the week. This allows for enhanced engagement in the ACT treatment. The digital platform will also track progress on Openness, Awareness, and Committed Action for participants and providers. Depending on a participant's progress in these three areas, the provider may recommend additional supplemental content as detailed in an ACT manual.

ACT Protocols for the Second Treatment Period

Participants who are initially randomized to ACT, depending on their response to treatment, will be assigned to either i) maintain ACT, ii) be randomized to ACT plus an augmentation therapy or iii) be switched to another treatment for the second treatment period. Participants assigned to maintain ACT (with or without a second augmentation treatment) will be encouraged to continue at-home skills and will have access to all previously viewed online content. In addition, participants will have access to 11 additional online ACT audio modules, but without the communications with the therapist. Participants assigned to switch will be recommended to stop at-home skills and will no longer have access to the online ACT content.

10.1.2.DOSING AND ADMINISTRATION

Week	Session Type	Activity
1	Remote face-to-face	**Visit 1**: Introduction Familiarize with online treatment
2	Therapist-supported online	**Session 1:** Shift Your Focus and What Will you Do?

2	Therapist-supported online	**Session 2:** Drop the Struggle and Act with Openness
3	Remote face-to-face	**Visit 2:** Review workbook, skills, goals; identify barriers
3	Therapist-supported online	**Session 3:** Act with Openness to Thoughts
3	Therapist-supported online	**Session 4:** Clarify Your Values, Define Your Goals, and Act
4	Therapist-supported online	**Session 5:** Focus on the Present Moment and Take Action
4	Therapist-supported online	**Session 6:** Build Further Engagement and Incorporate Barriers
5	Remote face-to-face	**Visit 3:** Review workbook, skills, goals; identify barriers
5	Therapist-supported online	**Session 7:** Commit, Act, and See You're the Observer-Self
6	Therapist-supported online	**Session 8:** Build Wider Patterns of Success
7	Remote face-to-face	**Visit 4:** Review workbook, skills, goals; close out treatment

Delivery of the online content is standardized given that all participants will view the same content, delivered in the same order to all participants. Delivery of the intervention by therapists will also be standardized. Therapists will receive a detailed manual covering the goals of the face-to-face sessions (in addition to online content) as well as a checklist for activities that should take place at each session. In addition, they will receive centralized training and certification, with periodic re-training, and will complete self-assessments. A 5% random sample of telehealth sessions per provider will be recorded and reviewed and evaluated for adherence and fidelity. At least once per month, and with greater frequency at the beginning of the study, all providers will meet with the central ACT provider who will support fidelity and competency in an effort to prevent drift.

10.1.3.ACQUISITION AND ACCOUNTABILITY

The ACT online platform will be HIPAA and FISMA compliant and will be hosted centrally on a University of North Carolina server. Participants assigned to ACT will have secure logins and passwords to access the site.

10.1.4.STUDY INTERVENTION COMPLIANCE

Adherence to the intervention will be assessed in terms of 1) attendance at each remote face-to-face session, 2) access and completion of each online module, 3) completion of exercises as recorded in the online platform, and 4) days of at-home skills practice as measured with the online workbook. Compliance with ACT treatment is defined as completion of at least half of the prescribed visits and modules. Participants completing fewer than 2 face-to-face visits or fewer than 4 online modules will be considered non-compliant.

10.2. STUDY INTERVENTION(S) ADMINISTRATION: DULOXETINE

Duloxetine hydrochloride is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is C18H19NOS0-HCl, which corresponds to a molecular weight of 333.88. Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) that is FDA-approved for use in cLBP and, as such, is included as a recommended therapy in nearly all current treatment guidelines for low-back pain and was selected by the Interventions Working Group as an evidence-based intervention to be included in this precision medicine study. 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.[13] There will not be a placebo arm for this intervention as this study is designed to optimize a precision medicine algorithm as opposed to investigate the effectiveness of duloxetine versus a placebo.

10.2.1. DOSING AND ADMINISTRATION

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is C18H19NOS0-HCl, which corresponds to a molecular weight of 333.88. Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

Each capsule contains enteric-coated pellets of 33.7 mg of duloxetine hydrochloride equivalent to 30 mg of duloxetine. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C Blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate.

Participants randomized to the duloxetine arm will review the dosing schedule for the medication and safety information for the medication at the baseline visit with the study coordinator. At the baseline visit a physical assessment will be performed. Certain sections must be completed by a licensed medical professional (e.g., MD, DO, FNP, PA, PT). Drug contraindications (including allergy to duloxetine, concomitant antidepressant use, concomitant tramadol use, liver disease, kidney disease, concomitant of St. John's wort use) will be reviewed with the participant. Participants reporting a history of bipolar disorder, manic episodes, or suicide attempts will not be randomized to the duloxetine intervention arm. Participants will also be counseled on seeking emergency help if suicidal ideation occurs while on duloxetine.

Participants will be treated with duloxetine for 12 weeks during the active treatment phase. At the time of randomization, the approved drug pharmacy at each study site will dispense between 185 and 192 duloxetine 30 mg capsules and provide to participants. This will ensure enough to maintain up to a 60 mg dosage through the 12-week intervention phase and to taper the dose in through the 14th week if needed.

Duloxetine will be started at 30 mg, orally once per day in the morning for the first 7 days. Study staff will conduct an assessment via phone on day 7 (or next business day if falls on a weekend) of the intervention phase with participants newly randomized to duloxetine (i.e., day 7 of either the first or second intervention period). Study staff will document in the case response forms any adverse events and safety concerns the participants may have.

At the Day 7 assessment:

Participants tolerating the medication with no side effects (e.g. nausea) will be escalated to 60 mg (two 30 mg capsules) by mouth once per day in the morning.

Participants tolerating the medication with mild side effects will have the option to stay at 30 mg or discontinue the medication.

Participants not tolerating the medication will be instructed to discontinue duloxetine. Participants in the first period intervention will be instructed to discontinue treatment until the next randomization point (Visit 1) at which time they will be randomized to a non-duloxetine second period intervention. Participants randomized to duloxetine in the second period intervention and not tolerating the medication will be instructed to discontinue duloxetine until their final follow-up of outcomes 24 weeks post baseline (Visit 2).

All participants will be provided with the site phone number and instructed to call if they have new or worsening side effects. If any safety or adverse events occur, the medication will be discontinued.

All participants will be assessed at the midpoint of the intervention treatment period (i.e., either Week 6 or Week 18) for tolerance, adverse events, and response. At the midpoint phone call:

Participants tolerating the medication with no side effects will be instructed to increase to 60mg/day (if currently taking 30mg/day) or remain on their current dosage (if currently taking 60mg/day).

Participants tolerating the medication with mild side effects (e.g. nausea) will be given the option of continuing their current dosage (30mg/day or 60mg/day), reducing their dosage (from 60mg/day to 30mg/day), or tapering off their current dosage (if currently taking 30mg/day).

Participants not tolerating the medication will be instructed to taper off the medication.

During the Week 18 call, participants will be reminded that their study treatment period is ending in six weeks. If they are tolerating the study medication and would like to continue duloxetine after the end of the treatment period, they should schedule an appointment with their provider to discuss continuing their duloxetine treatment outside of the study, in order to avoid a lapse in medication.

Tapering instructions:

The standard tapering period is up to two weeks. The following instructions will be provided to participants when they end their duloxetine treatment at either Visit 1 or Visit 2, or during the Week 6

or Week 18 calls. For participants who are taking 60mg daily, they will be instructed to reduce their dosage to 30mg per day for one week, and reduce to 30mg every other day for a week, as needed to reduce mild side effects. Participants taking 30mg per day can reduce their dosage to 30 mg every other day for up to 2 weeks, as needed to reduce mild side effects. At the discretion of the site PI or licensed designee, tapering can be extended an additional week, with the last dose no later than 21 days after Visit 1 or 2.

10.2.2.ACQUISITION AND ACCOUNTABILITY

Site staff will be responsible for ensuring study participants are instructed on how to return study medications and for tracking returned medication.

When medication is returned, site staff will count how many capsules are left and this number will be reported on the drug accountability log, and the remaining capsules will be disposed according to local, institutional policy.

10.2.3.FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Duloxetine hydrochloride is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Its chemical designation is (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride. The empirical formula is C18H19NOS0-HCl, which corresponds to a molecular weight of 333.88. Duloxetine hydrochloride is a white to slightly brownish white solid, which is slightly soluble in water.

10.2.4.PRODUCT STORAGE AND STABILITY

Medications will be procured from the approved drug pharmacy at each site to retain a supply to recruit at least 5 participants at a given time. Temperature in the storage room must be managed between 20 - 25°c (68-77°F); excursions permitted to 15-30°C (59-86°F) – per package insert. Medications may also be mailed to participant directly in the event of dispensing challenges (for example as related to the COVID pandemic). Sites must follow the guidelines outlined the Duloxetine Pharmacy Manual for mailing the study medication.

10.2.5.PREPARATION

30 mg capsule

10.2.6.STUDY INTERVENTION COMPLIANCE

Compliance with study protocol will be assessed by participant report and pill count. Participants will be required to return remaining medications to the study site at the time of their next in-clinic study visit (Visit 1 or Visit 2). Unused pills will be counted and documented at the site for accountability. At sites that mail the study medication directly to participants, these participants may be permitted to retain medication previously dispensed during Visit 0 if the medication is needed to ensure a medically appropriate transition. In these cases, unused study medication must be returned at Visit 2, instead of Visit 1, under certain conditions as described in the Duloxetine Pharmacy Manual.

Adherence to the intervention will be assessed in terms of 1) missed doses as reported by the participant and 2) number of capsules left in the returned medication bottle.

10.3. STUDY INTERVENTION(S) ADMINISTRATION: ENHANCED SELF-CARE

The content of the Enhanced Self-Care intervention is based on interventions which are currently available as part of many clinical practices but is formatted and structured in a manner that will provide multiple modules over the intervention period. The intervention is considered 'enhanced' in that most individuals with chronic pain do not receive an educational and self-care package. It is self-care given there will be no therapist associated with the delivery of these educational materials. The intervention will be provided digitally via multiple modules for self-administration over a period of 12 weeks. Each module will consist of evidence-based cognitive-behavioral self-management skills for pain. While all content is available to participants at all times, automated weekly email or text messaging will guide participants to specific content. Much of the material is derived from the current University of Michigan online self-management program called PainGuide.

PainGuide (https://PainGuide.com) is an educational website promoting the use of cognitive and behavioral self-management skills for chronic pain that is accessible online or by smartphone. PainGuide offers (A) education about pain, pain mechanisms, types of pain including chronic overlapping pain conditions (COPCs), and education about a wide variety of professionally administered pain treatments, (B) rationale and resources for using a variety of self-management approaches for pain, (C) a system for monitoring symptoms and self-management activities and (D) external resources supporting pain self-management.[54-57] Multi-media is used in communicating content including videos, text, audio files, apps, and downloadable worksheets. PainGuide is an expanded version of its predecessor FibroGuide, a similar digital pain self-management program with efficacy supported by clinical trials.[58] For the purposes of the proposed study, PainGuide has been adapted to the needs of patients with chronic low-back pain.

The Enhanced Self Care intervention arm will be comprised of three major components delivered via a single platform:

- Behavioral Self-Management– Established education and cognitive-behavior based self-management skills training and symptoms monitoring.
- Walking Program – a new module contained within PainGuide that offers a structured walking program that uses Fitbit devices for monitoring walking (e.g., Steps).
- Personalization and Engagement – ESC uses weekly automated email or text messaging to encourage engagement and to personalize the self-management content to be highlighted each week based upon participants' baseline surveys.

For this study, a customized version of PainGuide will be used. This version of the self-management website will include curated education and content targeted to a chronic low-back pain population. Two new modules have been added: a Walking Program utilizing Fitbit activity trackers for feedback and an over-the-counter (OTC) treatment module (e.g., NSAIDs and topical analgesics). The walking program will utilize Fitbit step tracking to allow participants to monitor their walking progress, while the OTC medication content will be educational in nature.

10.3.1. DOSING AND ADMINISTRATION

During the baseline visit, participants will be given a link for obtaining access to the version of PainGuide designed for this study. Access to this link will be provided after randomization and will require a username and password supplied by the study staff. 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 (Education). Study participants will be instructed to use this program for a period of 12 weeks. Though participants can choose to self-explore the material, there will be specific instructions delivered via text message or email that will direct participants to try the first few modules in a prescribed order: (1) Educational sections ("What is Pain" "Pain Mechanisms", and "Approaches to Pain Management," (2) Goal setting, (3) the Fitbit Walking program, and (4) OTC analgesics.

After the first four modules, email or text messages will be used to make personalized recommendations for accessing additional modules based upon identified problems from the baseline assessment using the PROMIS-29+2. For example, if sleep is identified as a problem at baseline, then the sleep module would be recommended for that individual. All materials will be available to the participant. This will allow participants to return to the materials for reinforcement or to access additional information not previously reviewed.

Most of the PainGuide modules focus on self-care, education and aerobic exercise (walking program). The PainGuide's educational module on medication has been adapted for BEST to provide a more detailed discussion of the use of self-administered over-the-counter (OTC) medications for chronic low-back pain. The medication module focuses on NSAIDs, which have been demonstrated to be an effective intervention in numerous cLBP trials and systematic reviews. Most of the discussion will be on NSAID oral medications such as ibuprofen and naproxen and the importance of consistent dosing. However, these medications are not tolerated by all individuals, and oral NSAIDs are contra-indicated for some cLBP patients, such as those with a history of gastrointestinal bleeding or who take oral anti-coagulants. Materials will stress the importance of the participant talking with their primary care or pain management provider in such circumstances. The module will also provide information on other OTC preparations such as oral acetaminophen, topical lidocaine or topical diclofenac.

The BEST trial's walking program module will build on PainGuide's pacing and self-care modules. Specifically, this module will provide guidance on the importance of aerobic exercise for cLBP as well as specific self-monitoring, goal-setting, and problem-solving education appropriate for cLBP patients. The module will provide strategies to counter maladaptive pain beliefs, especially fear avoidance regarding movement. All participants will be given a web-connected wearable device, Fitbit, to assist in monitoring their step count (a metric of functional status).

Participants will continue to have access to all of PainGuide modules throughout the trial. Use of the website will be captured passively with website utilization metrics. The online platform will also provide the participants tools to track their symptoms.

The Enhanced Self Care arm will be delivered via online self-management modules:

- Week 1: Educational content
    - What is Pain
    - Pain Mechanisms
    - Approaches to Pain Management
- Week 2: Goal setting
- Week 3: Fitbit walking program
- Week 4: OTC analgesics

- Weeks 5-12: Personalized recommendations (based on baseline, e.g., PROMIS 29+2, modules: (e.g., Sleep, Mood, Reframing)

ESC Protocol for Second Randomization Period

Participants randomized to continue receiving ESC in the second period intervention will receive personalized recommendations based on the most recently completed PROMIS 29+2.

10.3.2.ACQUISITION AND ACCOUNTABILITY

PainGuide is hosted centrally on a University of Michigan Server. Study staff at each participating site will be given the ability to establish personal accounts for each participant who is randomized to the ESC arm of the study.

10.3.3.STUDY INTERVENTION COMPLIANCE

Adherence to the intervention will be assessed in terms of 1) which modules were accessed by the participant over the course of the intervention period, 2) how long the participant spent on each module, 3) a questionnaire asking participants to provide feedback on their experience with the materials, and 4) number of days with login/activity.

10.4. STUDY INTERVENTION(S) ADMINISTRATION: EVIDENCE-BASED EXERCISE AND MANUAL THERAPY

Evidence-Based Exercise and Manual Therapy (EBEM) is provided by a licensed physical therapist or Doctor of Chiropractic. Evidence-based guidelines, including those from the American College of Physicians, the Agency for Healthcare Research and Quality, and the Departments of Defense and Veterans' Affairs, indicate that exercise and manual therapy are beneficial for persons with chronic back pain. Practice Guidelines and Systematic Reviews support benefits of exercise and manual therapy for persons with chronic LBP.[59,60]

Exercise and manual therapy interventions are most commonly provided to persons with LBP by physical therapists and Doctors of Chiropractic. Exercise helps patients with chronic LBP recover and avoid recurrence. Exercise has positive impact on both mental and physical well-being and will be included in every EBEM session. Evidence-based guidance is provided to direct decision-making on tailoring the particular type of exercise that is best-suited to each individual study participant.

Although systematic reviews have not found any specific type of manual therapy or exercise superior to another for all patients with LBP, there is support for decision-making strategies that describe how exercise and manual therapy interventions should be personalized to individual patients with LBP.

Evidence supports a multimodal approach combining exercise with manual therapy. Manual therapy is therefore included in each EBEM session. Evidence-based guidance is provided to direct decision-making on the particular type of manual therapy that may be best suited to an individual study participant. Special attention is paid to the clinician's choice of language in regard to the purpose and expected outcomes of manual therapy in order to avoid enhancing catastrophizing ideations or preference for passive interventions.

The EBEM intervention will train licensed physical therapists and Doctors of Chiropractic to personalize care to individual participants and enhance their effectiveness. These strategies are outlined below:

Risk Stratification

Risk stratification involves identifying physical and psychological factors associated with developing prolonged disability and providing treatments to address the specific risk factors present in an individual patient. The type and dosage of the EBEM treatment components (exercise, manual therapy and education) will be based on the participant's degree of risk. Training will provide guidance on how each of the treatment components can be tailored to participant's risk based on the results of the STarT Back Screening Tool collected at the baseline visit.

Intervention Tailoring

The core components of EBEM (exercise and manual therapy) will be tailored to address the unique needs of an individual participant. Training will focus on Treatment-Based Classification (TBC) as a decision-making framework with evidence to support its effectiveness. The TBC decision-making framework trains clinicians to tailor the particular selection of exercise and manual therapy techniques to individual patients with back pain.

Education Strategies

All participants will be helped to understand the biopsychosocial model of pain, which places emphasis on the important role of thoughts and attitudes as well as environmental factors on the pain experience. Key messages include the importance of remaining active and maintaining a positive outlook towards recovery. Education strategies are also designed to enhance participants' self-efficacy through motivation-enhancing communication and shared-goal setting procedures. Training will emphasize recommended communication strategies for establishing an optimal supportive and collaborative relationship with participants.

10.4.1. DOSING AND ADMINISTRATION

The EBEM intervention will be provided in face-to-face, one-on-one, sessions with a licensed physical therapist or Doctor of Chiropractic who has been trained in the intervention protocol. A total of 10 sessions will be provided over an 8-week treatment period. Two sessions per week are provided in the first two weeks followed by weekly sessions over the next 6 weeks. If visits are missed and/or need to be rescheduled, visits may be scheduled for up to 12 weeks. No more than 10 visits will be scheduled for participants newly randomized to EBEM in either the first or second intervention period. For participants maintaining EBEM in the second treatment period, no more than 4 visits will be scheduled. Treatment sessions will last approximately 60 minutes each.

Providers will be licensed PTs or DCs with at least 1 year experience working with patients with cLBP. Providers are required to attend 12 hours of training covering performance of specific techniques, adaptations to telehealth, risk stratification, tailoring, and participant education procedures. Some training content will be online.

Study providers will have their intervention visits monitored for fidelity via a video recording or in-person observation once they are certified to deliver the intervention. Fidelity assessments will be conducted with greater frequency during the early stages of enrollment and then as needed. Video recordings/observations will be reviewed/performed by investigators or designee and evaluated for the

criteria on a fidelity checklist. Fidelity assessments will focus on verifying that the exercise and manual therapy components were delivered as outlined in the protocol, and that no prohibited interventions were delivered. Individual providers will receive additional or remedial training in the intervention protocol whenever deficiencies in fidelity are observed.

EBEM Protocol for Second Randomization Period

Participants randomized to continue receiving EBEM in the second period intervention will receive 4 additional in-person EBEM sessions during weeks 1-4 of this period. If visits are missed and/or need to be rescheduled, visits may be scheduled up to 5 weeks from the date of the first augmenting/maintenance visit.

10.4.2.ACQUISITION AND ACCOUNTABILITY

Licensed Doctors of Chiropractic and physical therapists are eligible to be trained in the EBEM study protocol. Training will consist of a total of 12 hours of content covering the performance of specific exercise and manual therapy techniques as well as instruction in procedures for risk stratification, intervention tailoring using the TBC decision-making framework, and communication and motivation.

10.4.3.STUDY INTERVENTION COMPLIANCE

Adherence to the intervention will be assessed in terms of attendance to in-person sessions. Compliance with the first period EBEM treatment is defined as completion of at least 8 of the 10 prescribed visits. Compliance with the second period EBEM treatment is defined as completion of at least 3 of the 4 prescribed visits

10.4.4.MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The **first-stage randomization** will use a randomized version[61] of the Minimization method[62,63] to maintain marginal covariate balance. Minimization is an alternative to stratified permuted block randomization for maintaining (marginal) covariate balance across treatments that is better equipped to handle a larger number of factors to balance on. When a participant is randomized, a measure of the marginal discrepancy between treatments is calculated and the patient is randomized using a biased coin method where whichever treatment would make the discrepancy smallest has a higher probability and the other treatments have equal, smaller probabilities. Covariates included in minimization algorithm:

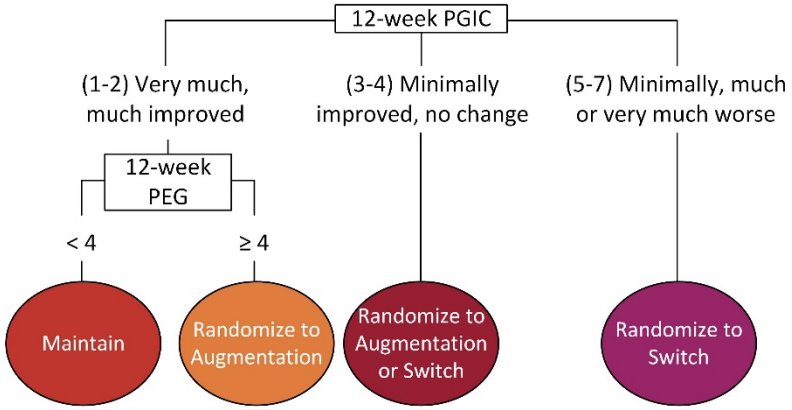
- Willingness to participate in deep phenotyping (yes/no)
- Depressive or anxiety symptoms (yes/no)
- Duration of pain symptoms (<5 years/≥5 years)
- Current use of opioid treatment (yes/no)

A total of approximately 740 participants will be randomized to ACT (n=185), duloxetine (n=185), ESC (n=185), and EBEM (n=185) and which will require recruitment of approximately 820 participants, anticipating that 10% will not be randomized due to failure to meet eligibility criteria at the end of the run-in phase and an estimated 15% will be lost to follow-up over the course of the study. Participants who did not complete required run-in procedures will not be randomized. 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.

Second-stage randomization will occur at the end of the first treatment period. Response to treatment will be assessed using the PEG and PGIC. Based on these scores, individuals will be grouped into 4 response classes.

- Group 1 participants (PGIC 1-2 and PEG <4) are assigned to **maintain** the first-line treatment.
- Group 2 participants (PGIC 1-2, PEG ≥4) are assigned to maintain the current treatment and **augment** with a randomly selected additional treatment.
- Group 3 participants (PGIC 3-4) are randomized to an **augmentation treatment or to switch** to a new treatment.
- Group 4 participants (PGIC 5-7) are randomly assigned to **switch** to a second-line treatment.



** Patients initially randomized to ESC with 12-week PGIC scores of 3-7 will be randomized to augmentation and not switching.*

Table 10.1 provides a list of all possible augmentations (combinations of the initial treatment with a second study intervention) and treatment switches for each of the initial treatment assignments. This randomization will be performed within initial treatment by using the minimization method[62,63] to achieve study-wide balance across treatments. Over the course of the study, the number and proportion of participants assigned to augmentation and switching overall, blinded to initial treatment assignment, will be monitored. If the proportions in each group differ meaningfully from the underlying assumptions used in the estimation of sample size, the proportion randomized to augment vs switch within Group 3 will be adapted to maintain power.

Table 10.1. List of all possible augmentations and treatment switching based on first-stage intervention.

First Stage Treatment	All Potential Second Stage Augmentations	All Potential Switches to Second Treatments
ESC	ESC + ACT ESC + Duloxetine ESC + EBEM	N/A
ACT	ESC + ACT ACT + Duloxetine ACT + EBEM	ESC Duloxetine EBEM
Duloxetine	ESC + Duloxetine ACT + Duloxetine	ESC ACT

	Duloxetine + EBEM	EBEM
EBEM	ESC + EBEM ACT + EBEM Duloxetine + EBEM	ESC ACT Duloxetine

Participants who must discontinue first-stage treatment early, regardless of their PGIC or PEG score, will be randomized to switch to a second treatment. These individuals will discontinue treatment and will be randomized to switch to a second-line treatment 12 weeks post baseline (Visit 1).

Randomization will be performed using the Carolina Data Acquisition and Reporting Tool (CDART), developed by the Collaborative Studies Coordinating Center at the University of North Carolina. CDART is designed and implemented as a centrally hosted, web-based, customizable and scalable data management system. Randomization algorithms will be developed by a biostatistician and custom-written in Java, which provides a full set of libraries and tools capable of complex algorithm implementation. This data management system will provide a means for implementing treatment allocation protocols, masking allocation of future participants, and for study staff to obtain allocation information immediately following randomization. Study staff and participants will not be blinded to treatment allocation given the nature of the interventions. Study investigators and staff involved in data analysis will be blinded to assignment.

Although patients and providers cannot be blinded with respect to study interventions, during the study data summaries produced for review by the study team that involve primary and secondary endpoint data will be blinded (e.g., treatment groups randomly permuted). Unblinded summaries may be required for review by the DSMB. Study team members involved in producing DSMB reports and/or presenting unblinded data to the DSMB will have no role in development of the study's statistical analysis plan.

11. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

11.1. DISCONTINUATION OF STUDY INTERVENTION

Early discontinuation of treatment is anticipated to be rare. Examples include a broken leg, precluding continuation of EBEM, or adverse reaction to duloxetine, necessitating discontinuation of duloxetine treatment.

11.2. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A participant may be discontinued from the study if he/she is shown to not meet the inclusion criteria based on new information that was not available at the time of initial enrollment and continuing in the study poses a safety risk (e.g., pregnancy or development of liver failure if on duloxetine). Participants should not be discontinued for reasons other than new information that constitutes a safety risk. For example, if new information indicates that a participant meets one of the exclusion criteria for an intervention, but the criteria does not pose a safety risk to the participant, then the participant should not be discontinued. In this case, the participant will be considered in violation of the protocol for that

period and excluded from the per protocol analysis (see Sections 10.1.4, 10.2.4, 10.3.4, and 10.4.4). In general, participants with poor compliance but at no increased risk will continue in the study to complete all study assessments and minimize attrition.

Other criteria for participant discontinuation at any point in the study:

- Participant meets one or more of the safety exclusion criteria defined in Section 8.
- Study physician determines that continuation in the study is not in the best interest of the participant.
- Participants can withdraw consent from the protocol at any point, and that will lead to discontinuation from the study. At that point, the investigator will make reasonable effort to ensure participant's well-being and safety and provide a termination visit with appropriate documentation.
- The site investigator may decide to stop a participant's treatment due to side effects or other safety concerns for the participant and/or site staff. If the participant is participating in the duloxetine intervention arm at the time of discontinuation from the entire study, the participant will be advised to taper their dose as outlined in Section 10.2. or obtain a prescription for duloxetine from their primary care physician or other provider.

11.3. LOST TO FOLLOW-UP

Participants who do not show up for a scheduled non-intervention study visit will be contacted by available means (calling, email, text). If an emergency number is provided, it can be used to contact the participant, at least to ensure they are doing well. Participants who fail to respond to voice and written requests to contact the clinical site and who miss the Baseline Visit or 12-Week Visit will be considered lost to follow-up. Participants who miss their 24-Week Visit will not be considered lost to follow-up and will be sent the 36-Week timepoint questionnaires. A termination form should be completed by the investigator to record the exit of any participant deemed lost to follow-up.

12. STUDY ASSESSMENTS AND PROCEDURES

12.1. EFFICACY ASSESSMENTS

Study outcomes will be assessed by self-report using a series of validated instruments to measure pain intensity and interference, physical function, depression, anxiety, sleep disturbance and duration, and opioid use. Patient-reported outcome measures will be administered at study baseline as well as at 12- and 24-weeks following first-stage randomization using a web-based survey platform. The primary endpoint is based on the Pain, Enjoyment of Life, and General Activity (PEG) scale, a 3-item assessment of pain intensity and interference with enjoyment of life and general activity over the past week. Response values for each item range from 0 to 10 and the average score across the three items will be used as the outcome value.

Secondary outcome assessments include:

- PROMIS Pain interference scale (PROMIS-PI, 4a)
- Current use of opioid medication on a daily basis
- PROMIS Physical Function (PROMIS-PF Short Form 6b)
- PROMIS 4-item Depression scale (from the PROMIS 29 profile)
- PROMIS Emotional Distress-Anxiety scale (PROMIS-EDA 4a)

- PROMIS Sleep disturbance (PROMIS short form 6a)
- Sleep duration (reported number of minutes asleep per night over the past month)

Primary and secondary endpoints

- **Primary endpoint: 24-week change from baseline in patient-reported pain intensity and interference**, measured with the Pain, Enjoyment of Life, and General Activity (PEG) scale at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in pain interference**, measured with the 4-item PROMIS Pain Interference scale (PROMIS-PI, 4a) at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **Incidence of opioid use,** measured by self-report at Visit 2 (24 weeks of treatment)
- **24-week change from baseline in physical function**, measured with the PROMIS-PF Short Form 6b at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in depression score**, measured with the PROMIS 4-item depression scale from the PROMIS 29 profile at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in anxiety score**, measured with the PROMIS Emotional Distress-Anxiety scale (PROMIS-EDA 4a) at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in sleep disturbance,** measured with the PROMIS short form 6a at Visits 0 (baseline) and 2 (24 weeks of treatment)
- **24-week change from baseline in sleep duration,** measured at Visits 0 (baseline) and 2 (24 weeks of treatment)

12.2. SAFETY ASSESSMENTS

Participants will be screened for contraindications to any of the BEST study interventions and phenotyping procedures prior to enrolling in the study. At the baseline visit, participant medical history will be obtained by the clinical coordinator and a physical assessment will be performed by a qualified medical professional. Basic safety assessments will be performed at 6 weeks (midpoint of intervention period one), 12 weeks (Visit 1), 18 weeks (midpoint of intervention period two), 24 weeks (Visit 2), and 36 weeks post-baseline (12 weeks after intervention period two) to assess participant tolerability to their current study intervention(s). Patients who are unable to tolerate their assigned study treatment will be educated on how to safely discontinue their current treatment plan but will otherwise remain in the study. Study staff will conduct an additional assessment of participants randomized to duloxetine via phone on day 7 (or next business day if falls on a weekend) of the intervention phase with participants newly randomized to duloxetine (i.e., day 7 of either the first or second intervention period).

Participants will be asked to report pregnancy status at multiple time points: prior to enrollment at Pre-screening and Screening, and prior to randomization at the Baseline and 12-Week visits. Participants who report pregnancy prior to randomization to the first period intervention are excluded from the study. If the participant becomes pregnant during the study, duloxetine will be rapidly tapered. Participants who become pregnant during the study will not undergo study MRIs.

12.3. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.3.1.DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human patient or research subject, including any abnormal sign (for example, abnormal physical assessment or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events occurring after the participant provides informed consent will be recorded.

12.3.2.DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death
- a life-threatening adverse event
- inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant and may require intervention to prevent one of the other outcomes listed in the definition above.

This definition permits either the sponsor or the investigator to decide whether an event is serious. Serious adverse events are critically important for the identification of significant safety problems. Therefore, if either the investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting (21 CFR 312.32(a) and 312.32(c)(1)).

12.3.3.CLASSIFICATION OF AN ADVERSE EVENT

Severity of Event

For adverse events (AEs), the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to study intervention

The site investigator is responsible for assessing the relationship between the AE and the study agent(s). Site investigators must provide the initial assessment as to whether there is a reasonable possibility that the study agent(s) caused or contributed to a SAE. The relationship assessment, based on clinical judgment, often relies on the following:

- A temporal relationship between the event and administration of the study agent(s),
- A plausible biological mechanism for the agent to cause the AE,

- Another possible etiology for the AE,
- Previous reports of similar AEs associated with the study agent or other agents in the same class, and
- Recurrence of the AE after re-challenge or resolution after de-challenge, if applicable.

Further assessment of causality is provided by the DSMB based on accumulating safety reports between treatment groups.

The terms used to assess the relationship of an event to study agent are:

- Related – There is a reasonable possibility that the AE may be related to the study agent(s).
- Not Related – There is not a reasonable possibility that the AE is related to the study agent(s).

Expectedness

Expected AEs are AEs that have been previously observed with the study intervention or procedures. An adverse event is considered "unexpected" if its nature, severity, or frequency is **not** consistent with either of the following:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

12.3.4.TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

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

A site physician investigator or sub-investigator will record all reportable events between the time the participant provides informed consent through 4 weeks after their last treatment. At each study visit,

the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution,stabilization, or participant is off-study.

12.3.5.ADVERSE EVENT REPORTING

Serious Adverse Event Reporting
Study investigators will immediately notify the DAC of any serious adverse event, whether or not considered test treatment-related, including those listed in the protocol or investigator brochure. The report must include an assessment of whether there is a reasonable possibility that the treatment caused the event.

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

- All AEs will be reported in aggregate to the NIAMS and the DSMB (through the NIAMS Executive Secretary) as part of the routine DSM report.
- All SAEs (regardless of relatedness or expectedness) will be reported to the NIAMS and the DSMB (through the NIAMS Executive Secretary) within 48 hours of the investigator becoming aware of the event.

12.3.6.REPORTING EVENTS TO PARTICIPANTS

Participants will be informed of any adverse events or serious adverse events if risk-benefit profile is impacted. Events significantly impacting the study integrity will require a change in protocol and additionally require re-consenting of participants. All active study participants would then be notified.

An abnormal finding may occur whenever imaging, conducting assessments, performing interventions, or completing study tasks. The purpose of imaging, assessments, and interventions are for research purposes only and are not intended to be used for clinical care (i.e., images will not be read by a radiologist). The imaging will not be read for clinical purposes and will not be reported to the patient (e.g., findings of spinal stenosis, neuroforaminal stenosis, lipomatosis, arachnoiditis will not be reported to the patient as the purpose is not for clinical care). During the course of the study, any gross abnormal finding noted in imaging or other assessment may be disclosed to the participant by the site investigator and the patient would be asked to follow-up with their Primary Care Physician (PCP). If the patient does not have a primary care provider, they will be instructed to establish care with a PCP to discuss further clinical management of the abnormal finding. Site investigators will work with DAC staff to notify participants and ensure that the patients are informed to follow-up with their PCP.

Examples of findings of clear clinical significance include:

- Abnormal blood pressure
- Intracranial abnormalities (e.g., hematoma, tumor)
- Intraspinal abnormalities (e.g., intraspinal tumors)
- Syncope during blood draws
- Pathological reflexes

Any other condition/finding in the discretion of the investigator that needs to be reported to the patient and assessed by a clinician/PCP.

12.4. UNANTICIPATED PROBLEMS

12.4.1. DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated Problem Involving Risk to Participants or Others (UPIRSO): Any incident, experience, or outcome that:

Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
Is related or possibly related to a participant's participation in the research; and
Is serious or suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

12.4.2. UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing IRB, as required, and to the DAC. The UP will be entered into the DMS and will include the following information:

A detailed description of the event, incident, experience, or outcome;

An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

All UPs will be reported to the NIAMS and the DSMB (through the NIAMS Executive Secretary) within 48 hours of the investigator becoming aware of the event.

13. STATISTICAL CONSIDERATIONS

13.1. STATISTICAL HYPOTHESES

The general objective of this study is to inform a precision medicine approach to cLBP. The statistical focus is on the estimation of a dynamic treatment regime (DTR) rather than to test the overall effectiveness of any single intervention or combination of interventions. The DTR will be estimated after the trial is completed, and it will use a panel of features, i.e. phenotypic markers, collected at baseline to recommend a first-line treatment, and then, depending on the response to treatment and any changes in participant covariates, recommend a second treatment (which may be a continuation of the first-line treatment). The performance will be measured by the estimated mean improvement in a given outcome (i.e. the PEG for the primary analysis) after two stages of treatment relative to baseline if the DTR were used to select treatments (called the value of the DTR). It is important to note that this goal

encapsulates discovering phenotypic markers that are associated with improved treatment response because the outcome is a function of the treatment received and a participant's covariates.

This section is intended to give an overview of the estimation targets for each study objective for the primary efficacy endpoint: the 24-week change from baseline in the PEG composite score. The PEG is a three-item scale with each item rated on a 0-10 scale. The mean response on these items will be used as the outcome.

The **primary objective** is to estimate an algorithm to assign sequences of two cLBP treatments based on phenotypic markers and an individual patient's response to the initial treatment (*i.e.,* a dynamic treatment regime) that optimizes effectiveness.

The goal is to estimate a DTR that maximizes the expected improvement in PEG after two stages of treatment relative to baseline. The estimation targets for this goal are 1) the parameters of the DTR and 2) the value of the estimated DTR.

To specify this formally, we will introduce notation from precision medicine (for a detailed review of this literature see Kosorok & Laber 2019).[65] Let X_1 denote the participant's covariates at the time of the first randomization, and X_2denote the interim data collected before the second randomization. A_t denotes the assigned treatment at the t-th stage randomization, and Y_t the difference between the PEG measured after completing the t-th stage course of treatment and the participant's baseline PEG score coded so that higher is better. Define H_t as the participant history available at the t-th stage randomization, so that $H_1 = (X_1)$ and $H_2 = (X_1, A_1, Y_1, X_2), and\ \boldsymbol{H} = (H_1, H_2)$. A dynamic treatment regime (DTR) is a sequence of functions $\boldsymbol{d} = (d_1, d_2)$ that maps participants to treatments based on the available history. An optimal DTR maximizes the expectation of a prespecified cumulative outcome $Y = f(Y_1, Y_2)$. In our case the outcome of interest is the 24-week change from baseline in PEG so $Y = Y_2$. The potential outcome under a regime $\boldsymbol{d}$ is given by

$$Y^*(\mathbf{d}) = \sum_{(a_1,a_2)} Y^*(a_1, a_2)\mathbf{1}(d_1(H_1) = a_1)\mathbf{1}(\mathrm{d}_2(H_2) = a_2)$$

where $\mathbf{1}$ is the indicator function that is equal to one when the condition is met and zero otherwise. The goal is to estimate $\mathbf{d}^{\mathrm{opt}}$, the DTR that maximizes the value function $V(\mathbf{d}) = E[Y^*(\mathbf{d})]$. The efficacy will be assessed in terms of the estimated value of the DTR $\hat{V}(\hat{\mathbf{d}})$. The optimal DTR, $\mathbf{d}^{\mathrm{opt}}$, is fundamentally unknowable in the same way that regression parameters are.

Secondary objective 1: Estimate DTRs that optimally balance multiple outcomes, taking into account participant preferences for outcomes including pain intensity, pain interference, physical function, opioid use, depression, anxiety, sleep duration and sleep disturbance.

A utility-based combination of multiple outcomes will be used Aim 2. These outcomes include level of pain, physical abilities, fatigue, anxiety, depressive symptoms, cognitive function, and overall enjoyment of life. Three combinations will be considered: 1) a combination of pain and physical abilities; 2) a combination of pain, physical abilities, and cognitive function; 3) a combination of all seven outcomes. By eliciting participant preferences between different outcomes, we can construct an optimal DTR that balances multiple competing outcomes and respects the relative importance of these outcomes to each participant (Butler et al). Future treatment decisions could be informed by administering the preference

elicitation tool in combination with the estimated DTR to guide treatment decisions. Participant preferences will be elicited at baseline through a series of discrete choice tasks, and participant satisfaction with treatment will be measured after each stage of treatment to help calibrate the preference estimation. The efficacy will be assessed in terms of the estimated value, or expected patient-tailored combination of outcomes, of the DTR. $\hat{V}(\hat{\mathbf{d}})$.

Secondary objective 2: Estimate DTRs that incorporate additional phenotypic markers (i.e., deep phenotyping) collected on a sub-set of participants.

Secondary objective 3: Assess whether effectiveness is sustained based on outcomes collected 24 weeks after randomization to the second treatment.

The change in the PEG composite score collected 24 weeks after the start of the second treatment relative to baseline will the efficacy endpoint for Secondary objective 3. This is identical to the primary efficacy endpoint except with a longer follow-up time. The efficacy will be assessed in terms of the estimated value of the DTR $\hat{V}(\hat{\mathbf{d}})$.

Exploratory objectives: Evaluate the (1) comparative effectiveness of individual treatments; (2) comparative effectiveness of different treatment regimes (i.e., a particular regime with a given set of rules at each decision point); and (3) impact of treatment order on outcomes.

We can test the null hypothesis that the value of two different DTRs are equal. Let $\mathbf{d}^0$ denote the best DTR that does not consider a participant's phenotype (the best zero-order DTR). This DTR assigns every participant the treatment with the best population average treatment effect. Let $\mathbf{d}^{\text{opt}}$ denote the optimal DTR that considers participant phenotype. We can conduct two-sided tests of superiority of the hypothesis

$$H_0: \mathbf{V}(\mathbf{d}^0) = \mathbf{V}(\mathbf{d}^{\text{opt}})$$
$$H_1: \mathbf{V}(\mathbf{d}^0) \neq \mathbf{V}(\mathbf{d}^{\text{opt}})$$

For the other interventions that are not the best, we can analogously define a DTR that always recommends each of these treatments and compare them to each other and to the optimal DTR.

13.2. SAMPLE SIZE DETERMINATION

Simulation Methodology Overview

Simulation studies were used to determine the sample size for the trial using a grid search over potentially feasible sample sizes. The outcome measure was the difference in PEG at 24 weeks relative to baseline. The performance metric of interest in the simulation studies was how close the value of the estimated dynamic treatment regime, $V(\widehat{\mathrm{d}_n})$, was to the value of the optimal dynamic treatment regime $V(\mathrm{d}^{\text{opt}})$ for the difference. The percentage of optimal value is equal to $V(\widehat{\mathrm{d}_n})/V(\mathrm{d}^{\text{opt}})$ (assuming $V(\widehat{\mathrm{d}_n})$ is non-negative and $V(\mathrm{d}^{\text{opt}})$ is strictly positive). Note that this is not a hypothesis test but a performance criterion that evaluates how close the estimated treatment regime is to the optimal treatment regime

The estimated value of the estimated dynamic treatment regime for each replicate was obtained using Monte-Carlo methods and an independent out-of-sample data set. First, an out-of-sample data set was

generated using the same data generating distribution as the one used to generate the trial data for a given simulation scenario. A dynamic treatment regime is estimated on the replicate study data using Q-learning.[5,6] Then for every dynamic treatment regime, the estimated DTR is used to assign the out-of-sample participants to treatment sequences, and the estimated value of the DTR calculated (the expected outcome under each treatment is known for all out-of-sample participants). Finally, the ratio of the value from estimated DTR to the optimal DTR is calculated.

The analog to power in this setting is the probability that the ratio of the value from a DTR estimated on a trial with sample size n relative to the value of the optimal DTR is greater than or equal to a fixed performance cutoff δ.

$$P\left(V\left(\widehat{\mathrm{d}_n}\right) \div V(\mathrm{d}^{\mathrm{opt}}) \geq \delta\right)$$

We chose a performance cut-off δ of 0.9, so that for a simulated trial to be considered a success the value of the DTR estimated on that simulation replicate's data must be within 90% of the optimal DTR's value.

There is no analog to Type-I error for this because a null scenario would imply that all treatments are equally ineffective and no biomarkers matter, and in this situation any dynamic treatment regime is trivially optimal.

Simulations were conducted using R version 4.0.4

Simulation Data Generation

The outcome after each stage, Y_t the outcome is defined as the difference in PEG between the follow-up visit at the end of the stage and the baseline PEG. The simulation outcomes are on the standardized effect size scale instead of the 0-10 scale. The outcome of interest, Y, is the difference in PEG at 24 weeks relative to baseline $Y = Y_2$,.

Let $A_{t,k}$ denote the indicator function $\mathbf{1}(\text{Intervention } k \text{ given for stage } t)$ that is one whenever intervention k is given for stage t and zero otherwise. For the outcome after each stage, Y_t , denote the conditional expectation of Y_t given the history and intervention by $Q_t(H_t, A_t) = E[Y_t|H_t, A_t]$. Then the data generating model for one of the simulation scenarios with a single covariate associated with the outcome is:

$$\begin{aligned}
Q_1(H_1, A_1) &= .1A_{1,0} + .25A_{1,1} + .3A_{1,2} + .4A_{1,3} + .3X_1A_{1,3} + .25X_2 - .25X_3 \\
Q_2(H_2, A_2) &= .1A_{2,0} + .25A_{2,1} + .3A_{2,2} + .4A_{2,3} + .3X_1A_{2,3} - .1A_{2,1}A_{2,2} - 1A_{2,1}A_{2,3} \\
&\quad - .1A_{2,2}A_{2,3} + .25X_2 - .25X_3 \\
Y_1 &= Q_1(H_1, A_1) + \epsilon_1, \quad \epsilon_1 \sim N(0,1) \\
Y_2 &= Q_2(H_2, A_2) + \epsilon_2, \quad \epsilon_2 \sim N(0,1) \\
Y &= Y_2
\end{aligned}$$

Recall that in the first stage exactly one intervention can be given, while in the second stage one or two interventions may be given.

The covariates were generated independently with $X_1 \sim \mathrm{Bern}(.5)$, $X_l \sim \mathrm{Bern}(p_l)$, $\mathrm{l} = 2, \ldots, 5$ where and p_l ranges from 0.5 to 0.9 and X_l are coded to take values $\{-1, 1\}$ instead of $\{0, 1\}$ and an additional five normally distributed covariates $N(0, .5)$. There were a total of ten covariates, one of which was

associated with the outcome through a treatment interaction, and two prognostic covariates that influence the outcome but was not associated with response to treatment. The Q-functions were estimated using mis-specified models that included interaction terms for every treatment by covariate pair, and the models were fit by the Lasso.

These settings give rise to the following optimal rule:

X_1	A_1^{opt}	A_2^{opt}	Response to treatment at 24 weeks compared to baseline
$X_1 = -1$	Any intervention	$A_{2,1}$ and $A_{2,2}$ in combination	0.45
$X_1 = 1$	Any intervention	$A_{2,2}$ and $A_{2,3}$ in combination	0.9

The optimal rule above, $\mathbf{d}^{\text{opt}}$, has an average (over the values of X_1) response of (0.45+0.9) = 0.675. An example DTR with a value that is within 90% of the optimal value is:

X_1	A_1^{opt}	A_2^{opt}	Response to treatment at 24 weeks compared to baseline
$X_1 = -1$	Any intervention	$A_{2,1}$ and $A_{2,2}$ in combination	0.45
$X_1 = 1$	Any intervention	$A_{2,1}$ and $A_{2,3}$ in combination	0.85

Which assigns $A_{2,1}$instead of $A_{2,2}$ as part of the combination for biomarker positive patients in stage two. The average response (over the values of biomarker X_1) is 0.65.

The table below shows $\mathbf{d}^{\text{opt}}$and other treatment rules for comparison.

Treatment Regime	Average response to treatment at 24 weeks compared to baseline
$\mathbf{d}^{\text{opt}}$ (incorporates phenotypic markers)	0.675
Assign A_0 in both stages	0.1
Assign A_1 in both stages	0.25
Assign A_2 in both stages	0.3
Assign A_3 in both stages	0.4
Assign A_3 in the first stage and $A_{2,2}$ and $A_{2,3}$ in combination in the second stage (no phenotypic markers)	0.6

The probability of attaining a value within at least 90% of the optimal value for this scenario is 81% based on 5,000 replicates (Monte Carlo standard error ≈ 0.009)

The treatment effect sizes were based on systematic review by the Agency for Healthcare Research and Quality[18,59] and an internal review conducted by the experts on BACPAC's Interventions Working Group. The standardized treatment effect sizes were assumed to be 0.25 for ACT, 0.3 for Duloxetine, and 0.4 for EEMT. The effect size for enhanced standard of care was assumed to be 0.1. Subgroup-specific effects were constrained so that the population average treatment effect was equal to the effect sizes from the systematic review.

Simulation Results

A total of 630 complete cases yields 80% probability to attain a value within at least 90% of the optimal value. Assuming ~15% of participants fail to complete the study through the primary efficacy endpoint, a total sample size of approximately 740 randomized would be sufficient to achieve at least 90% of the possible reduction in PEG 80% of the time. The 15% drop-out is intended as an upper-bound, not the actual anticipated drop-out, and is based on a threshold provided by experts in this area where they would have serious concerns about any study having above this rate of drop-out.

13.3. POPULATIONS FOR ANALYSES

All participants

The "All participants" population will consist of all participants consented to the study.

All Randomized Population

The All Randomized population will consist of all participants randomized and statistical analyses will follow the intention to treat approach as much as possible. The All Randomized population will be used in primary, secondary, and exploratory analyses.

13.4. STATISTICAL ANALYSES

13.4.1.GENERAL APPROACH

Below we provide an overview of the general statistical approach planned for this trial. A complete and detailed statistical analysis plan (SAP) will be completed prior to any evaluation of primary or secondary outcome data stratified by treatment group or sequence.

The primary goal will be to estimate a two-stage dynamic treatment regime that maximizes the expected reduction in PEG between the beginning and the end of the study. We will use Q-learning for this approach.[5] Q-learning reduces the reinforcement learning problem of optimizing a two-stage dynamic treatment regime to a standard regression problem, after which standard regression algorithms can be applied. A secondary interest will be to estimate a two-stage DTR that minimizes some combination of multiple outcomes, where the ideal trade-off is estimated using participant preferences. Here we will use a latent variable approach: We will assume that that the optimal combination, or preferred trade-off, of outcomes for each individual can be represented as a simple convex combination of outcomes, where the participant-specific weights of the convex combination are unobserved and depend on the participant's covariates and responses to questionnaires. To estimate and make inferences on these weights, we will estimate the posterior distribution of these latent weights conditional on the covariates and questionnaire responses. This is what was proposed, for example, in Butler 2016.[67] Other objectives include assessing long-term effectiveness of embedded and estimated treatment regimes and conducting hypothesis tests to compare the effectiveness of individual treatments and nested treatment regimes. Comparisons of first-stage treatments and of second-stage treatments adjusted for first-stage treatments can be conducted using standard t-tests. Comparisons of nested DTRs can be conducted using the methodology discussed in Kosorok and Moodie

2016.[68] Estimation and assessment of DTRs based on longer-term outcomes can be conducted using Q-learning. The methods used for conducting inference and variable importance analysis of the Q-functions will depend on the data at hand and the regression procedures chosen. However, one possible contender is the bootstrapping method of Chakraborty, Laber and Zhao 2013.[69]

We expect missing data to be minimal because of study procedures discussed previously to enhance retention such as incentives, incorporation of patient stakeholder feedback in the development of study materials, and efforts to minimize participant burden. In addition, there will be ongoing participant engagement through a study website, contact with research staff and regular patient engagement efforts. Finally, protocols for discontinuation of study treatment that are not tolerated are planned to enhance retention. We will continue to follow all participants until the end of the study and will utilize alternative forms of data collection for those who do not attend planned study visits (e.g., telephone administration or online data collection). Despite these efforts, missing data will arise and, as needed and appropriate, will be addressed using non-parametric multiple imputation procedures. Sensitivity analyses will be presented in detail as part of the SAP.

13.4.2.ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Complete details will be provided in the formal Statistical Analysis Plan for the study.

13.4.3.ANALYSIS OF THE SECONDARY ENDPOINT(S)

Complete details will be provided in the formal Statistical Analysis Plan for the study.

13.4.4.SAFETY ANALYSES

No safety analyses are planned other than descriptive summaries and data listings of reported adverse events.

13.4.5.BASELINE DESCRIPTIVE STATISTICS

Complete details will be provided in the formal Statistical Analysis Plan for the study.

13.4.6.PLANNED INTERIM ANALYSES

No interim analyses are planned for the study. Adaptation to the design, *i.e.* the second stage randomization probabilities, is planned and details will be included in a future Statistical Analysis Plan. Briefly, overall proportions of participants assigned to augment or switch will be monitored. If proportions deviate meaningfully from assumptions, we will consider shifting randomization probabilities within Group 3 (*e.g.*, from 50/50 to 60/40 augment/switch).

13.4.7.SUB-GROUP ANALYSES

N/A

13.4.8.TABULATION OF INDIVIDUAL PARTICIPANT DATA

Complete details will be provided in the formal Statistical Analysis Plan for the study.

13.4.9.EXPLORATORY ANALYSES

Complete details will be provided in the formal Statistical Analysis Plan for the study.

14. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

14.1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

14.1.1. INFORMED CONSENT PROCESS

Potential participants will be asked to provide consent to the protocol at the Enrollment Visit through a master consent document. Our general approach to the consent process is to explain the design of the master protocol to each potential participant, why this design will assist with understanding how to better match future cLBP patients to the most appropriate treatment(s) based on their individual characteristics, lifestyle, and environment and optimize their outcomes, how participation in the protocol will allow participants to receive treatment(s) that have been independently shown to clinically improve pain intensity and interference and may improve other outcomes such as function, why their participation is important, and how their data will contribute to the research. The goal is to obtain buy-in from potential participants on the study expectations and requirements as a whole and explain clearly what they can expect from participation in the study (e.g., expected study duration given their enrollment date, possibilities of participating in two different treatments or remaining in one treatment assignment throughout the study, etc.). The master consent form provides details about the possible treatment(s) each potential participant may receive.

The master consent document describes the intervention process and procedures involved in the BEST trial. Participants will be informed that their consent will allow them to be assigned to a treatment, which may be augmented or changed during the intervention period. If they are not willing to provide consent, they are not eligible for the study.

Note that participants will also be asked to consent to storage of and future use of their data and biospecimens separately from their consent to study participation. Participants will be able to consent to the study (including use of biospecimens in BEST) but opt out of having their data and biospecimens stored for future use. Participants will also have the option to be considered for participation in more comprehensive phenotyping procedures, which include brain MRI, quantitative sensory testing, and an advanced spine MRI.

Each consented participant will receive a signed copy of the study consent. The site's signed consent form copy is to be filed with other confidential participant information. Upon completion of the consenting process, each participant's informed consent information is entered into the data management system for study tracking purposes. During the study, consent information is updated in the data management system when the participant notifies the study that they would like to modify their consent or withdraw from the study. After study completion, participants may not be able to modify their consent for biospecimen use because all remaining biospecimens will be transferred the NIH biospecimen repository which will control access to the biospecimens.

This study will be reviewed under a single institutional review board (IRB) at Advarra®. All sites will rely on the Advarra® IRB, and a reliance agreement, either an IRB Authorization Agreement (IAA) or SMART IRB agreement, will be established for each site institution. If an institution has a master service agreement established with Advarra®, a study-specific IAA will not need to be established. Once fully executed, a copy of the IAA, SMART IRB agreement, will be submitted to the DAC, with the original agreement filed on site. If the institution is under a master service agreement with Advarra®, the site will need to supply a copy to the DAC. The DAC will ensure that every consent form meets federal

requirements and presents accurate information, as determined by the protocol team and NIH regulatory officials, and the current consent form will be kept on file and available for review.

In obtaining and documenting informed consent, BEST study investigators and study teams will comply with applicable regulatory requirements, namely, ICH, GCP and other regulatory requirements including Title 45 Part 46 of the Code of Federal Regulations (45 CFR 46), 21 CFR 11 (Electronic Records), 21 CFR 50 (Protection of Human Subjects), 21 CFR 54 (Financial Disclosure of Clinical Investigators), 21 CFR 56 (Institutional Review Boards), and 21 CFR 312 (Investigational New Drug Application).

14.1.2.CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting administration of the study intervention. The following consent materials are submitted with this protocol:

- Adult Consent Form_English

Basic consent elements and appropriate additional elements as outlined in 45 CFR §46.116 and 21 CFR §50.25 include:

- Statement that the study involves research;
- Explanation of the purposes of the research, the expected duration of the subject's participation, and a description of the procedures to be followed;
- A statement of the conditions and period of time under which the participant's data will be stored and will be accessible;
- A description of any foreseeable risks or discomforts to the participant;
- Reasonably expected benefits to participant or others;
- Disclosure of alternative procedures;
- Confidentiality measures;
- Explanation of compensation and medical treatment, if any, for injury;
- A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits and that the participant may discontinue participation in any time without penalty or loss of benefits; and
- An explanation of whom to contact for answers to pertinent questions about the research and research participant's rights, and whom to contact in the event of a research-related injury to the participant, for research questions, or for questions about rights.

Additional elements include:

- Unforeseeable risks to the participant and/or to the fetus or embryo in case of pregnancy;
- Circumstances under which participation may be terminated without regard to participant's consent;
- Additional costs to participant resulting from study participation;
- Consequences of the decision to withdraw and procedures for orderly termination of participation by the participant;
- New study findings which may affect the participant's decision to continue; and
- Approximate number of study participants.

Informed consent form requirement for clinical trials:

The FDA and NIH have mandated that all informed consent documents inform participant volunteers that trial data will be added to the national clinical trial registry databank at ClinicalTrials.Gov. The exact wording to be included in the documents reads: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

14.1.3.CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator or study coordinator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. In cases where a participant is required to be re-consented, re-consent may also be obtained remotely with prior permission from the DAC. In this case, the consent form will be provided to the participant. It will be reviewed with the participant over the phone or during a video call. The participant may sign the consent form and return it to the site, or the form may be signed electronically, provided a software tool that is compliant with the Code of Federal Regulations (CFR) 21 Part 11 concerning electronic signatures is available at the site. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

14.1.4.STUDY DISCONTINUATION AND CLOSURE

The trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (see examples below). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, the NIAMS, the Food and Drug Administration and other relevant regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator at each study site will promptly inform study participants, the IRB, and the 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. Please refer to Section 11, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy NIAMS, the IRB and/or other regulatory agencies.

14.1.5.CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study documentation, data, and all other information generated will be held in strict confidence.

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

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

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

Study participant research data used for purposes of statistical analysis and scientific reporting will be securely transmitted to and stored at the DAC. The study data entry and study management systems used by clinical sites and by the DAC will be secured and password protected (see Sections 5.2.3. and 14.1.11.)**.** At the end of the study, data will be de-identified and sent to an NIH data repository.

Certificate of Confidentiality

To further protect the privacy of study participants, a Certificate of Confidentiality (COC) has been automatically issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14.1.6.FUTURE USE OF STORED SPECIMENS AND DATA

BEST will be collecting specimens on all participants. Strict confidentially standards are in place and will be maintained to protect the privacy of study participants. Biospecimen samples will be labeled with a unique identifier that does not contain any protected health information or otherwise identify a participant. Biospecimens collected will not be stored long-term at the clinical sites but rather will be deposited in batches at the NYU Langone Health Center for Biospecimen Research and Development (CBRD). These specimens will not be individually identifiable by the laboratories, clinical centers, or DAC personnel. The DAC will develop and maintain a tracking system whereby study participants can modify their level of consent for their use of any stored samples for future studies. Participants can ask that any specimens still in storage be destroyed and not included in future analyses.

Genetic studies utilizing the participant's DNA will be conducted in BEST. Other "omics" studies will also be conducted in BEST. These may include studies to evaluate the RNA transcriptome and the microbiome, and they could potentially include studies involving the metabolome, the epigenome, and the proteome. Data collected for this study will be analyzed and stored in the secure servers at the DAC and submitted to the secure cloud-based data portal at the DAC per the schedule defined in the BACPAC Data Transfer SOP. After the study is completed, the de-identified data will be transmitted to and stored at an NIH-approved repository for use by other researchers including those outside of the study. Permission to transmit data to the NIH repository will be included in the informed consent.

With the participant's approval and as approved by the study's single IRB, de-identified biological samples will also be stored at a NIH's HEAL repository after the study is completed. These samples could be used for future research.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed. When the study is completed, access to study data and/or samples will be provided through the NIH data and biospecimen repositories.

14.1.7. KEY ROLES AND STUDY GOVERNANCE

The BEST Executive Leadership Committee (ELC) will provide leadership for the implementation of the BEST trial and will serve as the primary decision-making body regarding actions taken in response to challenges that arise implementing the study protocol. Membership will include the BEST Protocol Co-Chairs, the BEST Project Manager, the NIAMS BACPAC Program Coordinator, and two BEST site PIs (serving on a rotating basis). Primary duties of the ELC will include interacting with NIH regarding the progress of the trial towards key milestones, facilitating the BEST Operations Committee (OC) meetings, and providing high-level reporting on the trial to the BACPAC Steering Committee at regular intervals. The ELC will also be responsible for determining whether protocol modifications are needed and for seeking input/approval from the BACPAC Steering Committee as needed.

The BEST OC will provide feedback to the ELC regarding the conduct of the study. OC bi-weekly meetings will provide a forum for site PIs to share implementation successes and challenges with the broader set of OC members to foster refinement of best practices regarding conduct of the study. Membership will include ELC members, BEST site PIs, NIH/NIAMS representatives, and BEST intervention experts, as well as experts from the BACPAC Adaptive Design Expert Group, Intervention Working Group, Deep Phenotyping Working Group, and Theoretical Model Working Group.

14.1.8. SAFETY OVERSIGHT

NIAMS will establish an independent Data and Safety Monitoring Board (DSMB) charged with oversight of data quality, study integrity, and safety of participants. Per NIAMS requirements, all SAEs regardless of the expectedness and relatedness must be reported to the NIAMS and the DSMB through the NIAMS Executive Secretary within 48 hours of the investigator becoming aware of the event.

AEs are reported in aggregate and presented at the semi-annual DSMB meetings. The DSMB will review unblinded data reports semi-annually and make recommendations to the NIAMS to ensure that

participants are not exposed to undue risks. The DAC will submit a summary report of recommendations after each DSMB meeting to the central IRB. After IRB review, the summary of recommendations will be distributed to the site investigators to store with study documentation.

The DSMB will make recommendations as to whether an intervention or the entire study should be stopped for safety reasons based on periodic monitoring of adverse events and other safety parameters. Regularly scheduled DSMB meetings will be held to review safety data reports prepared by the DAC that include summary statistics by treatment group for adverse events, laboratory parameters, and other safety outcomes. Ad hoc DSMB meetings to review safety data can also occur if triggered by unusually high or unexpected SAE reporting.

Once a determination is made to recommend discontinuation of the study or a specific intervention for safety reasons, the DSMB's deliberations and rationale for arriving at the recommendation will be shared with the PI and key personnel. The DAC will prepare a report for the NIAMS Project Officer and the Operations Committee that summarizes the results of analyses supporting the recommendations, the stopping boundaries or rules used, and the DSMB's summary of their deliberations to arrive at the decision. The DAC will then work with the Operations Committee to develop an appropriate communication plan for the various stakeholders.

DSMB Members

Members of the DSMB are independent experts chosen by NIAMS on the basis of their expertise and scientific rigor. They are not associated with the trial or with the pharmaceutical companies that supply the study agents. Committee members' areas of expertise span the disciplines relevant to the conduct of this clinical trial, including clinical trials, pharmacology, biostatistics, and clinical care of participants with cLBP.

DSMB Mandates

The DSMB has the responsibility to review the research protocol and other study materials and to evaluate the progress of the trial overall and at each participating clinical center. This includes accrual, data quality and completeness, episodes of exacerbations, hospitalizations, mortality, other toxicities, and protocol violations. NIAMS expects expedited reporting of SAEs, Unanticipated Problems, and Protocol deviations that impact participant safety to occur within 48 hours of the investigator becoming aware of the event. Protocol deviations that occur but do not affect participant safety are submitted in aggregate as part of the routine DSMB meeting report.

Concurrently, the DSMB will evaluate the safety of the interventions studied under the Protocol as the trial progresses, considering evolving scientific discoveries or treatment options that may affect the desirability of continued treatment with any one of the interventions. At the conclusion of each meeting, the DSMB will recommend whether the study or specific interventions be continued. If the intervention proves to be more harmful than expected in terms of mortality or severe morbidity, the treatment of all participants will be stopped and the intervention arm closed to study enrollment. This decision will be made by NIAMS on recommendation of the DSMB.

Frequency of DSMB Meetings

The DSMB will meet via webinar approximately every 6 months to review study progress and safety. The schedule of meetings will be determined during the first meeting. These meetings will likely take place via webinars, due to the need to schedule them at different times for different interventions. Ad hoc

meetings may also be scheduled via webinar if particular safety issues for any of the interventions arises in between the regularly scheduled meetings.

DSMB Meeting Structure

The BEST principal investigators, the DAC statisticians (blinded and unblinded), NIAMS representatives, and, on occasion, other key personnel will participate in the meetings' open sessions. Open sessions will include but not be limited to consideration of recruitment, retention, and general scientific issues. The DSMB's voting members will discuss the unblinded by-treatment data for each intervention in a closed session. These data include but are not limited to adverse events, and material that should be kept confidential from the investigators.

Frequency and content of reports to the DSMB

In advance of each meeting, the unblinded statistician at the DAC will prepare a report for DSMB review. The report will contain the following categories of information aggregated by treatment group, where applicable, as well as any additional information required by the DSMB:

- Current enrollment status and timeline for completion of follow-up
- Adverse events reported, both serious and non-serious, including hospitalizations and any mortality
- Major and minor protocol violations and deviations
- Numbers of participants whose study medication is discontinued

Decisions on the labeling of treatment groups in the safety reports and other considerations to lessen the chance of accidental unmasking will be determined at the first meeting of the DSMB. The unblinded DAC statistician will provide the treatment for each code to DSMB members as needed, and the same code mapping will be used for all meetings.

Serious events are reported to the NIAMS within 48 hours of the investigator becoming aware of the event.

Frequency, content, and distribution of meeting reports

Following each meeting of the DSMB, the meeting recommendations and open meeting minutes are drafted by the NIAMS Executive Secretary and include, but are not limited to, questions raised by the DSMB, monitoring recommendations, and recommendations for the continuation of treatments or the study as a whole. These minutes are reviewed and approved by the DSMB and NIAMS. The NIAMS executive secretary will prepare a summary of the questions raised by committee members, monitoring recommendations, and recommendations for the continuation of treatments. The meeting recommendations and minutes will be distributed confidentially to meeting participants. The NIAMS executive secretary also prepares a closed session minutes (if applicable) for distribution to BEST investigators and their IRBs.

14.1.9.CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of study participants are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with International

Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring for this study will be performed by the DAC.

Areas of Focus

- Staff training
- Human subjects protection
- Protocol compliance
- Regulatory compliance
- Laboratory SOPs and compliance
- Quality assurance (QA)
- Safety
- Adverse event reporting
- Integrity of research data and samples

Two types of data monitoring will be conducted during the study: on-site monitoring and central monitoring. On-site monitoring refers to a review of the data that takes place at the clinical site whereas central monitoring refers to activities that can be conducted at the data coordinating center.

Monitoring Activities will include:

- Review of credentials, training records, and delegation of duties logs
- Review of 100% of Consent Forms
- Review of reports on missed events, missing data, protocol deviations, and unanticipated problems
- Comparison of CRFs to source documentation to ensure data are accurate and complete
- Review of documentation for AEs, SAEs, and UPs
- Review of critical fields such as eligibility, study endpoints, and SAEs
- Regulatory Files: Limited reviews at interim visits, e.g., IRB annual reviews, safety reporting, IRB submissions of protocol deviations, and updated essential documents
- Laboratory Review: Full laboratory review of processing and storage of specimens at first and close-out visits and at least biannually. Assessment of laboratory specimens stored at the clinical site

The DAC will provide copies of on-site monitoring reports within 10 business days of the visit.

Details of clinical site monitoring will be documented in the BEST Clinical Monitoring Plan (CMP). The CMP will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

14.1.10. QUALITY ASSURANCE AND QUALITY CONTROL

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

Quality control (QC) procedures will be implemented beginning with the data entry system. The database will include real-time data QC checks. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

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

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

Magnetic Resonance Imaging (MRI) Quality Control of Brain Images

Even when comparable hardware and experimental procedures are employed in brain imaging studies with functional magnetic brain imaging (fMRI) and structural MRI, between-site variability may arise. This may come from a number of sources including: small flaws in data collection equipment/software, subtle differences in experimenters' administration of standardized protocols, and differences between scanner brands. It is not possible to quantify these variables using non-human models (e.g., brain MRI phantoms). To control for these variables, the same member of the BEST Trial MRI domain expert's research team will travel to each trial site. This study member will undergo MRI scan protocols that are identical to the phantom scans. These scans include: structural T1 brain image, resting state brain image, and diffusion tensor structural brain image. Performing these scans on the same human at each trial site will allow researchers to identify, measure, and minimize inter-site variability among MRI scanners. Data from these scans will not be included in the BEST Trial dataset.

14.1.11. DATA HANDLING AND RECORD KEEPING

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DAC. The study data entry and study management systems used by clinical sites and by the DAC will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at an NIH-approved data repository.

Risk of disclosure will be minimized through the use of several procedures. The DAC operates under FISMA (Federal Information Security Management Act) guidelines, and the data management system used in BEST is compliant with FDA 21 CFR Part 11, which establish security policies for the study databases, such as requiring use of strong passwords, limiting access to data based on study role, and the use of secure sockets layer encryption during data transmission. The data management system database is encrypted at rest using a FIPS 140-2 certified cryptographic system. Within the data management system, data elements are persisted in a format which isolates personal identifying information from other data elements.

14.1.12. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

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

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MEDDRA) and concomitant medications will be coded using the National Drug Code (NDC) Directory.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into CDART, a 21 CFR Part 11-compliant data capture system managed by the DAC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.1.13. STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of research in accordance with HHS regulations. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of NIAMS. It is the responsibility of the study sponsor to inform the investigators when these documents no longer need to be retained.

14.1.14. PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the study protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

Protocol deviations require reporting to the DAC, and to the oversight IRB, and additional source/supporting documents may be requested and should be kept in the participant's record. Sites should notify the DAC in accordance with the Manual of Procedures.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 48 hours of identification of the protocol deviation, or within 15 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents and reported to the DAC. Protocol deviations must be sent to the reviewing IRB per their policies, as applicable. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.1.15. PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the BACPAC DAC Data Portal Protocol, Data Transfer SOP, BACPAC Data Access and Publications Policy, and the following publication and data sharing policies and regulations:

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

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this study 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 researchers at the discontinuation of BACPAC by contacting the NIH-approved HEAL repository.

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), SNP arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

The BACPAC Data Access and Publications Committee will be responsible for developing publication procedures and resolving authorship issues.

14.1.16. CONFLICT OF INTEREST POLICY

The independence of the BEST study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of investigators who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, investigators who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIAMS has established policies and procedures for investigators to disclose all conflicts of interest and has established a mechanism for the management of all reported dualities of interest.

14.2. ABBREVIATIONS

ACT	Acceptance and Commitment Therapy
AE	Adverse Event
BACPAC	Back Pain Consortium Research Program
CBRD	Center for Biospecimen Research and Development
CDART	Carolina Data Acquisition and Reporting Tool
CFR	Code of Federal Regulations
cLBP	Chronic Low-Back Pain
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CPM	Conditioned Pain Modulation
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DAC	Data Integration, Algorithm Development and Operations Management Center
DC	Doctor of Chiropractic
DSMB	Data Safety Monitoring Board
DTR	Dynamic Treatment Regime
EBEM	Evidence-Based Exercise and Manual Therapy
eCRF	Electronic Case Report Forms
EHR	Electronic Health Record
ESC	Enhanced Self Care
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HEAL	Helping to End Addiction Long Term Initiative
HIPAA	Health Insurance Portability and Accountability Act
IAA	IRB Authorization Agreement
ICH	International Conference on Harmonisation
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IND	Investigational New Drug Application
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
NCT	National Clinical Trial
NDC	National Drug Code
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	National Institutes of Health
NSAID	Non-Steroidal Anti-Inflammatory Drug
OC	Operations Committee
PEG	Pain, Enjoyment of Life, and General Activity
PGIC	Patient Global Impressions Scale

PHI	Protected Health Information
PI	Principal Investigator
PRO	Patient Reported Outcome
PT	Physical Therapist
QA	Quality Assurance
QC	Quality Control
QST	Quantitative Sensory Testing
RSS	Radiation Safety Sub-committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMART	Sequential, Multiple Assignment Randomized Trial
SNRI	Serotonin Norepinephrine Reuptake Inhibitor
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
UPIRSO	Unanticipated Problem Involving Risk to Participants or Others

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16. SURVEY QUESTIONNAIRES

Abbreviated Pain Somatization
Current Opioid Use
Daily Pain Question
Demographics
FABQ-PA scale
NHANES Food Frequency*
GAD-2
GSS-8
HEAL Resilience
Hip/Knee replacement
Low-Back Pain Duration
Low-Back Pain Frequency
Low-Back Pain Specific Pain Intensity
Michigan Body Map
Oswestry Disability Index
Pain Catastrophizing Scale SF 6
Pain, Enjoyment of Life, and General Activity (PEG)
PainDETECT
Patient Global Impressions Scale (PGIC)
Patient Preference for Outcome
Patient Preference for Treatment
Patient Satisfaction with Outcomes
PHQ-2
PROMIS 29+2 / PROPr
Radicular Pain
Sleep duration
Social Determinants of Health
SSI (symptom severity index)
StartBack Tool
TAPS 1
Treatment Categorization
Widespread Pain Inventory

*Will be piloted and may be removed from study protocol if it is determined to cause excessive participant burden

17. APPENDIX A: SCHEDULE OF ACTIVITIES

Schedule of Activities: National Institute of Arthritis and Musculoskeletal and Skin Diseases, (NIAMS) - BACPAC - 21-1972, The BEST Trial: Biomarkers for Evaluating, Spine Treatments (Pro00057948)***

	Pre-Screening	Enrollment Visit	Run-in Week 1	Run-in Week 2	Post Run-In Screening	Visit 0 (Baseline)	Visit 0 (Baseline optional day 2)	Week 1	Week 2	Week 3	Week 4	Week 5	Phone Call1 (week 6)	Week 7	Week 8	Week 9	Week 10	Week 11	Visit 1 (Week 12)	Visit 1 (Week 12 optional day 2)	Week 13	Week 14	Week 15	Week 16	Week 17	Phone Call 2 (week 18)	Week 19	Week 20	Week 21	Week 22	Week 23	Visit 2 (Week 24)	Visit 2 (Week 24 optional day 2)	Phone Call 3: Safety follow-up (week 28)	Phone Call 4: Observational follow-up for subset (week 36)**
EMR Review/ Interview/ Pre-screen eligibility	X																																		
Low-Back Pain Duration Q'naire	X																																		
Low-Back Pain Frequency Q'naire	X																																		
Low-Back Pain Intensity	X				X								X						X						X						X			X
Low-Back Pain Severity Q'naire	X				X														X												X			X
PEG	X				X								X						X						X						X			X
Eligibility Assessment Questions	X	X				X							X						X						X						X			
Demographics	X	X																																
Informed Consent		X																																
Contact Information Form	X	X																																
Schedule study visits	X	X				X													X															
Review of study informational materials		X				X													X															
Introduction/ Onboarding to patient website		X																																
Introduction/ Onboarding to Run-In		X																																
Daily Pain Questions			X	X																														
Post run-in assessment					X																													
Sleep duration Question						X													X												X			X
Abbreviated Pain Somatization						X													X												X			X
Radicular Pain Questions						X													X												X			X
FABQ-PA scale						X													X												X			X
GSS-8						X																												
Pain Catastrophizing Scale SF 6						X													X												X			X
PHQ-2						X													X												X			X
GAD-2						X													X												X			X
TAPS 1						X													X												X			X
Social Determinants of Health						X																												
Perceived Discrimination						X																												
HEAL Positive Outlook						X													X												X			X
PROMIS 29+2 / PROPr						X													X												X			X
Treatment Categorization Q'naire						X													X												X			X
StartBack Tool						X																												
SSI (symptom severity index)						X																												
Widespread Pain Inventory						X													X												X			X
Current Opioid Use						X													X												X			X
ODI						X																												
Satisfaction overall ranking						X													X															
Satisfaction with treatment																			X												X			X
COVID vaccination status question						X													X												X			X
COVID previous diagnosis question						X													X												X			X
Michigan Body Map						X																												
PainDETECT						X																												
Patient Preference Tool						X													X												X			X
Food Frequency Questionnaire						X																												
Physical Assessment						X													X												X			
Randomization to 1st period Intervention						X																												
Blood collection						X													X												X			
Stool collection						X	x*																												
Biomechanical assessment (light)						X	x*												X	x*											X	x*		
Basic Spine MRI						X	x*																												
Activity monitoring (deep)						X	x*																												
Biomechanical assessment (deep)						X	x*												X	x*											X	x*		
Advanced Spine MRI						X	x*																												
Brain MRI						X	x*												X	x*											X	x*		
Quantitative Sensory Testing						X	x*												X	x*											X	x*		
PGIC													X						X							X					X			X
Intervention tolerance assessment/ Adverse Events													X						X							X					X			
End-of-study safety assessment																																	X	
Randomization to 2nd period Intervention																			X															
Scheduling/Introduction/Onboarding to 2nd period Activities																			X															

Schedule of Activities: The BEST Trial: Biomarkers for Evaluating, Spine Treatments (Pro00057948)***

Intervention-specific contact points	First treatment period														Second treatment period (maintenance subset)												
ACT intervention-specific contact points	X		X		X		X																				
Duloxetine intervention-specific contact points	X														X												
EBEM intervention-specific contact points	X	X	X	X	X	X	X	X							X	X	X	X									
ESC intervention-specific contact points																											

** If not completed on day 1 of the visit*

*** Participants who are enrolled early enough to complete the 36-week assessments*

**** Refer to Manual of Procedures for Visit Windows*