Mechanisms of Psychosocial Treatments for Chronic Pain

Study Protocol

Version Date: March 15, 2022

IRB Title: Back on Track to Healthy Living Study
Short Title: Back on Track (BOT) Study
NCT Number: NCT03687762

Mechanisms of Psychosocial Treatments for Chronic Pain

A randomized, 3-group parallel design, 240-subject clinical trial to test the mechanisms of cognitive therapy, mindfulness meditation, and activation skills on individuals with chronic pain.

Study Chairman or Principal Investigator:

Mark P. Jensen, Ph.D., Professor and Vice Chair for Research, University of Washington Department of Rehabilitation Medicine

Melissa A. Day, Ph.D., Senior Lecturer, University of Queensland School of Psychology

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TOOL REVISION HISTORY

Version 7.32
Version Date: March 15, 2022
Summary of Revisions Made:

1. Updated DSMC Chair from Dr. Jirikowic to Dr. Brown.

Version 7.31
Version Date: October 19, 2021
Summary of Revisions Made:

1. Per request of UW IRB, updated section F4g. Safety Review Plan of protocol to be consistent with NCCIH-approved DSMP version 3.4, which had the same exact changes approved on June 16, 2021.

Version 7.3
Version Date: March 24, 2021
Summary of Revisions Made:

1. Added Shreya Pakalpati, Nikki Torres, Andrea Newman, and Emily Goldberg to and removed Kevin Gertz from Study Team Roster and Blinded/Unblinded Research Staff.
2. Changed Andrea Thomas from Blinded to Unblinded Research Staff.
3. Removed “UW Department of Rehabilitation Medicine” from exclusion criteria “current or past participation in a UW Department of Rehabilitation Medicine research study with treatment components that may overlap those in the current study” so that any study with overlapping treatment is exclusionary, regardless of where study is from.
4. Fixed an error in Figure 1. Study Design that screening may be done ≤ 6 months before randomization; this was corrected to ≤ 3 months.
5. Age, sex, gender, race, and ethnicity data may be collected after informed consent prior to the start of the Pre-Treatment Phase.
6. Revised D6a. Recruitment: expanded recruitment sources and revised language to be more flexible.
7. Added exception to when a resource list is provided to ineligible participants.
8. The collection and retention of assessment data outside the defined assessment window is allowed if that assessment had been started by the participant within window.
9. The collection and retention of assessment data collected outside window, if that assessment had been started within window, will not be considered a protocol deviation.

Version 7.2
Version Date: April 27, 2020
Summary of Revisions Made:

1. Removed Sam Battalio and Hannah Lessing from protocol, as both departed the study and our institution in fall 2019 to pursue graduate studies.
2. Updated titles for Emily Stensland and Andrea Thomas, due to promotions.
3. Removed ActiGraph Compliance Monitoring Period and reduced the number of ActiGraphs mailed out from two to one. Participants will now be compensated $70 for the return of one ActiGraph versus $20 for the first ActiGraph and $50 for the second.
4. Moved 3- and 6-month follow-up assessments to be completed online by the participant.
5. Added items on COVID-19’s effects on mental health and well-being to extended assessments and the Qualitative Interview.
6. Added providing participants with a study schedule.

7. Added flexibility for contacting participants regarding missed EMAs and ActiGraph non-wear, due to the variability in participants' participation level and individual circumstances.
8. Lowered the randomization threshold of EMA survey completion from 10/14 EMAs to 7/14 EMAs during Week 1 of the Baseline Monitoring Period.
9. Removed ActiGraph Compliance Monitoring Period from required baseline procedures for randomization.
10. Removed limit on number of people enrolled for each cohort.
11. Removed limit on number of people in each treatment group.
12. Added language describing who may cover a treatment session if an emergency arises.
13. Added an email option to the Replacement Check Protocol.
14. In Table 3, corrected the number of items administered in the EMAs and extended assessments for the PAS, CSQ, PCPQ, and pain-related self-efficacy; this was researcher oversight in updating the table to reflect the number of items currently being administered and analyzed. Also corrected sub-scales for SOPA measure, added PGIC and PGATS measures to Tertiary Outcomes (researcher oversight), additional COVID-19 items to Exploratory Moderators, and additional cannabis use items to Secondary Outcomes.
15. Added COVID-19 items, cannabis use items, and additional details to various measures in Table 4.

Version 7.1
Version Date: January 31, 2020
Summary of Revisions Made:

1. Added Calia Morais to Study Team Roster and Blinded/Unblinded Research Staff.
2. Revised window for re-assessment of pain interference (asked to ensure that pain interference still meets study entrance criteria) from 4 weeks to 5 weeks before start of Baseline Monitoring Period.
3. Added flexibility to setting a participant's morning and evening EMA windows, should the participant be unable to utilize the study's pre-determined EMA windows.
4. Increased the maximum number of participants staff can enroll per cohort from 36 to 40.
5. Corrected omission in Table 3 – employment status and weight change questions are also asked at Baseline.
6. Expanded study clinicians to include those with a Masters-level degree or higher.

Version 7.0
Version Date: December 12, 2019
Summary of Revisions Made:

IMPORTANT: Items #1, 3-4, 6-9, 11-13, 17-18, 22-23, and 31 were verbally approved by NCCIH PO and committee during a phone meeting on 10/7/19. Permission was granted by NCCIH that day to proceed with those verbally approved changes to the protocol. Changes that were not approved in that earlier version of 7.0 but were discussed during the NCCIH meeting had their tracked changes removed from this current version, thus removing any indication they had ever been proposed. Since the 10/7/19 meeting, the study team has included additional revisions to this later version of 7.0, indicated in tracked changes throughout. These new tracked changes are both due to the findings from the Westat IMV on 9/4-9/6/19 as well as some independent of that visit.

1. Added Andrea Thomas, Kala Phillips, and Madison Sherwood to Study Team Roster and Blinded/Unblinded Research Staff.
2. Updated phone numbers for staff in Study Team Roster.

3. Removed requirement that participants must have a formal “diagnosis” (e.g., as indicated on a medical record) of chronic pain; however, participants must still meet criteria for having chronic pain per the NIH Low Back Pain Task force guidelines.
4. Revised randomization scheme to a covariate-adaptive approach.
5. Per phone meeting with NCCIH PO and committee on 10/7/19, removed inclusion criteria “Pain is consistent (pain is either always present or present most of the time, with only occasional periods of no pain, if any)” as this was confusing with inclusion criteria “Meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in past 6 months)”.
6. Added exclusion criteria of having a terminal illness.
7. Added exclusion criteria of inability to walk (defined as unable to walk at least 50 yards).
8. Added exclusion criteria of significant pain from a recent surgery or injury.
9. Removed blanket exclusion of autoimmune conditions; revised to having a serious medical condition that may interfere with study participation or with receiving potential treatment benefits.
10. Per phone meeting with NCCIH PO and committee on 10/7/19, added explicit statement specifying that all materials and procedures to be used for recruitment will be submitted to the University of Washington IRB for review and approval.
11. Added flexibility to clinic recruitment by removing requirement to send out an initial approach letter or email to patients prior to approaching them in clinic.
12. Added in-person efforts in clinics and other spaces, public ads, and print, online, and media advertisements as recruitment options.
13. Removed “diagnosis” verification process that involved accessing medical records or requiring a completed form from the participant’s health care provider.
14. Clarified that re-screening for study eligibility will also be done if the screening questions are revised and the participant has not yet been randomized. Staff will re-screen participants on the most current approved version of the screening questions.
15. Per Westat site monitor during IMV on 9/4-9/6/19, removed letter of orientation from protocol. A physical letter is not being used as all enrollment information is emailed to the participant.
16. There was a typographical error in D6c. Consent Process that stated the informed consent process may only be done if within 7 weeks prior to the start of the treatment groups for that particular cohort – this was inconsistent with other areas of the protocol stating informed consent could occur up to 6 months before randomization. We revised D6c. to be consistent with other areas of the protocol. However, such subjects will be rescreened to ensure they meet inclusion / exclusion criteria.
17. Clarified baseline and demographic information may be collected again if collection is not within 3 months of randomization.
18. Clarified a refresher technology training will be done if participant does not participate in the treatment groups for the cohort which s/he completes the initial technology training. In other words, the technology training will be done again so that it is within the cohort that the participant will receive the intervention.
19. Removed option for participants to wear ActiGraphs on the ankle.
20. Lowered the ActiGraph wear compliance percentage during the ActiGraph Compliance Monitoring Period from 70% to 50%.
21. Added option to re-contact participants who do not meet baseline criteria for EMA completion or ActiGraph compliance, should the cutoffs for these criteria change in the future.
22. Increased the number of study cohorts per year.
23. Clarified the maximum number of participants enrolled per cohort.

24. Clarified that homework submission will be done electronically, specifically via Google Drive.
25. Formally defined treatment completion as attending at least 4 out of 8 sessions in an intervention.
26. Added details on Intent-to-Treat (ITT) process. Per phone meeting with NCCIH PO and committee on 10/7/19, we have revised the details to explicitly state that no deferrals to a future cohort will be allowed for participants after they have been randomized.
27. Clarified that qualitative interviews will not be conducted for participants who do not attend any treatment sessions.
28. Corrected typographical error in Table 3 that incorrectly listed Treatment Credibility items being assessed during Extended assessments.
29. Per Westat site monitor during IMV on 9/4-9/6/19, removed "X" from Table 4. Study Assessment Schedule for PROMIS Pain Interference being assessed at the Baseline time point – this was a typographical error.
30. While reviewing Table 4 with Westat site monitor on 9/4-9/6/19, staff caught another error in this table, where "X"s were left off Employment Status and Weight being assessed at the Baseline time point. These omissions have been corrected.
31. Changed Jeffrey Borckardt from blinded to unblinded staff member, due to needing his expertise to help manage unblinded data.
32. Per phone meeting with NCCIH PO and committee on 10/7/19, provided more detail in table listing blinded and unblinded staff regarding the activities they will engage in. Included specifics clarifying that investigators who oversee study data may still listen to unblinded fidelity recordings and participate in final data analysis. Provided rationale for this allowance and noted when this permission was granted by the PO.
33. Per Westat site monitor during IMV on 9/4-9/6/19, added statement explicitly stating that participant non-completion of study components should not be counted as protocol deviations and included the date the NCCIH PO granted permission for this.
34. Revised re-screening window for inclusion/exclusion from 6 months to 3 months, per recommendation of NCCIH PO and committee.
35. Added verbiage to D6r. Data Collection and Management attesting that staff performing data collection/participant evaluations will not be analyzing and reporting study outcome data during the data collection phase of the study. Blinded/Unblinded Research Staff table updated.

Version 6.0
Version Date: June 5, 2019
Summary of Revisions Made:

1. Expanded the population to broadly include participants with chronic pain. Participants must also endorse having low back pain as a primary or secondary pain problem.
2. Added exclusion criteria of headache as primary pain condition.
3. Removed exclusion criteria of having another confounding chronic pain condition.
4. Outcomes collected specifically about low back pain changed to chronic pain.
5. Added additional flexibility to recruitment contact methods and contact order.
6. Added departmental Participant Pool and previous studies as recruitment source.
7. Revised verification of diagnosis procedures from verification of low back pain diagnosis to more broadly verification of a chronic pain diagnosis.
8. Added flexibility in randomization eligibility, such that exceptions to meeting all eligibility criteria may be made on a case-by-case basis.
9. Added option for participants to complete their home practice activities through electronic, cloud-based forms (e.g., Google Drive forms).

10. Clarified qualitative interviews will be coded by a transcription company and not research staff.

Version 5.1
Version Date: March 1, 2019
Summary of Revisions Made:

1. Changed both co-PIs from blinded status to unblinded status.
2. Added Emily Stensland as a staff member.
3. Added anxiety and PTSD measures to extended telephone assessments. This was an oversight, as researchers had planned to add all measures from this study's Administrative Supplemental to this Primary grant.
4. In Table 3. Primary, Secondary, Co-Variate, and Mechanism Variables, distinguished between Medication Use questions and Medication Use Attitudes questions.
5. Clarified when staff may call participants to check on stabilized medications during the screening process.
6. Changed EMA compliance cutoff from 85% to 80% such that the DSMC Chair may call a meeting with study investigators should EMA completion compliance fall below 80%.
7. Updated page numbers in Table of Contents.

Version Number: 5.0
Version Date: December 28, 2018
Summary of Revisions Made:

1. Revised screening criteria to be more consistent with NIH Low Back Pain Task Force's recommended questions. This changes the inclusion criteria slightly as now a participant's LBP must have been a problem for them at least 50% of the time in the past 6 months whereas before a participant must only have experienced LBP at least 50% of the time in the past 3 months. Additionally, we added a pain consistency requirement to ensure participants who meet eligibility criteria do not have sporadic/episodic pain. These pain consistency and frequency questions were also added as criteria to the Pain Interference Re-Assessment.
2. Broadened the exclusion criterion regarding planned surgery to include all planned surgeries, rather than those exclusively related to the low back.
3. Adjusted recruitment sources to allow for broader scope. This includes clinics that are not directly affiliated with the University of Washington system, as well as the use of social media, online forums, websites, patient advisory networks, and expanded use of referrals.
4. The screening window was expanded to allow up to 6 months between self-report screening and randomization.
5. Clarified text surrounding the diagnosis verification process to accommodate for additional means (email, fax) for sending the Release of Medical Information form between prospective participants.
6. Corrected the phrasing of the EMA window description to allow participants to choose from one of three options.
7. Changed when staff may randomize participants from 8 days after the start of Baseline Monitoring to as early as 6 days, as we realized a participant could theoretically become eligible for randomization as early as Day 6.
8. Added pain medication belief questions to Baseline Assessment and Extended Telephone Assessments, as well as treatment preferences questions to Baseline Assessment.

9. Revised length of Optional Assessments from 10-20 minutes to 20-30 minutes to accurately reflect time it takes to complete optional questions.
10. Clarified that participants may email their session homework directly to clinicians.
11. Clarified that 25% of all treatment sessions will be rated for treatment fidelity instead of 30%, as 25% results in an even number of sessions (i.e., 25% of 8 sessions is 2, whereas 30% of 8 is 2.4). Revised fidelity to be done following the end of treatment for each cohort, as time constraints prevent fidelity from being done in parallel with treatment.
12. Added Jennifer Altman, Erica Wasmund, and Laurel Peabody to Study Team Roster and D6r. Data Collection and Management (Blinded/Unblinded Research Staff). Corrected roles for Elena Mendoza and Sam Battalio in D6r. Dr. Mendoza will not be involved in randomization at all while Sam, due to an increase in need for unblinded staff, has switched from a blinded to unblinded role.

Version Number: 4.2
Version Date: July 25, 2018
Summary of Revisions Made:

1. Added Sydney Drever to Study Team Roster and D6r. Data Collection and Management (Blinded/Unblinded Research Staff).
2. Revised D6k. Randomization with additional details per NCCIH OCRA comments.
3. Corrected eligibility criteria and corresponding medical record review and self-report screening protocols.

Version Number: 4.1
Version Date: June 21, 2018
Summary of Revisions Made:

1. Added audio-recorded treatment sessions may be used for training purposes.
2. Revised suicide protocol to state that clinical assessments for suicidality may be conducted by post-doctoral level clinicians who are under the supervision of licensed, credentialed, and privileged providers.

Version Number: 4.0
Version Date: June 15, 2018
Summary of Revisions Made:

1. Added IRB and short titles for study.
2. Changed Zoom training session to technology training session; participants will be provided instruction in use of all study technologies, not just the Zoom application.
3. Added re-assessment of low back pain interference for general activities; participants need to score a minimum of ≥3 for the past 3 months in order to be eligible for randomization.
4. Added low back pain interference assessment (Roland Morris Disability Questionnaire, RMDQ) to be administered to participants prior to Baseline Monitoring Period to determine randomization stratification.
5. Added ActiGraph Compliance Monitoring Period to occur one week immediately prior to Baseline Monitoring Period; participants must return activity monitor with wear time of 70% or higher to be eligible for randomization.

6. Added exclusion criteria “current or past participation in a UW Department of Rehabilitation Medicine research study with treatment components that may overlap those in the current study”.
7. Added allowable windows to study assessments and procedures which did not already contain windows; updated all windows to reflect addition of ActiGraph Compliance Monitoring Period.
8. Revised study timeline to account for delayed study start.
9. Updated informed consent section to state researchers have obtained a Waiver of Documentation of Informed Consent.
10. Added additional question to EMA survey asking participants whether they uploaded their completed homework activities into the EMA system.
11. Revised the number of ActiGraph return points from three to two.
12. Increased the total payment amount for ActiGraph return from $50 to $70.
13. Removed secure messaging via the EMA system as a method of participant contact.
14. Revised randomization scheme and procedures.
15. Revised number of cohorts per year to reflect updated SARP, Version 2.0.
16. Corrected length of mindfulness meditation practice recordings from 45 to 40 minutes.
17. Updated Tables 3 and 4 to be consistent with latest items on assessments.
18. Corrected random selection of treatment fidelity recordings from 30% to 25%.
19. Added additional severity level to scale for grading adverse events.
20. Revised procedures for documenting regulatory events (AEs, SAEs, and unexpected problems), AE reporting, and SAE reporting.
21. Revised frequency of review of safety data by the DSMC to be consistent throughout.
22. Revised regulatory event reporting IRB documentation will be stored electronically instead of hard copy form.
23. Updated Appendix: Evaluation Timeline with Pain Interference Re-Assessments.
24. Updated page numbers in Table of Contents.

Version Number: 3.0
Version Date: March 29, 2018
Summary of Revisions Made:

1. Updated D6r. Statistical Analyses, D6s. Missing Data, and D6t. Power Analyses with minor clarifying language and additional references.
2. Updated STUDY TEAM ROSTER with contact information for new staff member Hannah Lessing.
3. Updated D6q. Data Collection and Management “Blinded/Unblinded Research Staff” table with new staff member Hannah Lessing.
4. Updated E4e. Mental Health Issues / Suicidality with minor language revisions.
5. Added five additional citations to References.
6. Updated page numbers in Table of Contents.

Version Number: 2.0
Version Date: February 6, 2018
Summary of Revisions Made:

1. Updated PRÉCIS with objectives and hypotheses presented in more general terms.
2. Updated A2a. Primary Aim and Hypotheses and A2b. Secondary Aim and Hypotheses with objectives and hypotheses presented in more general terms.

3. To limit potential confusion, removed four conceptual models from A2. Specific Aims and Hypotheses. A new SEM model was added to D6r. Statistical Analyses; this new model illustrates how the study aims and hypotheses will be tested.
4. Added ActiGraph wear compliance of 70% of time or higher during Week 1 of the Baseline Monitoring Period as an additional condition for randomization.
5. Deleted four figures from protocol, added one new figure, and re-numbered figures throughout.
6. Added measurement of activity level and activity monitor wear questions to daily EMA survey.
7. Added research staff will request participant to have information statement with them during consent process.
8. Added letter of orientation provided to participants following consent process.
9. Added a sentence describing the security of the EMA software.
10. Removed all references to CentrePoint, a cloud-based ActiGraph study management software platform. Participants will no longer submit ActiGraph data daily to this software platform; instead, all participants will be required to mail back their current devices at three time points: after the first week of the 2-Week Baseline Monitoring Period, after the end of the Treatment Monitoring Period, and at the end of the 4-Week Post-Treatment Monitoring Period. Compensation of up to $50 will be provided if the participant returns his/her ActiGraph for all three time points.
11. Added the procedure that research staff will monitor ActiGraph wear compliance through questions on the EMA survey.
12. Added additional information regarding repeating the 2-Week Baseline Monitoring Period at the time of the future cohort in the instance that a participant defers after starting the Monitoring Period before getting randomized.
13. Added the option of providing participants a copy of their ActiGraph summary data at study completion, should they be interested and request a copy.
14. Added language stating research staff will contact participants who do not return their ActiGraphs within a reasonable amount of time.
15. Clarified that participants will be randomized no sooner than eight days after the start of the 2-Week Baseline Monitoring Period.
16. Added unblinded staff member may also send the participant part or all of their participant treatment handbook prior to the first session.
17. Updated the maximum number of participants per group from ten to twelve in the event that all enrolled participants for a cohort become eligible for randomization.
18. Updated method for which participants will submit their completed home practice forms from email to the EMA management system.
19. Changed home practice forms as collected for referential purposes only to study data (home practice data will be extracted from these forms).
20. Added information regarding ActiGraph wear compliance to D6m. Study Design Enhancements: Treatment Fidelity, Missed Sessions and EMA Assessments, Participant Engagement, and Study Retention Strategies.
21. Updated compensation to include up to $50 for ActiGraph return at three time points.
22. Added language describing attempts to reach participants research staff are unable to get a hold of during the course of the study.
23. Updated Tables 3 and 4 with activity level measures in EMA survey.
24. Updated D6q. Data Collection and Management with procedures on ActiGraph mail-ins for data collection; updated “Exceptions to Separation of Study Data from Identifying Information” with change that home practice forms will now be collected via the EMA management system with engagement in home practice data extracted and stored.

25. Revised D6r. Statistical Analyses with initial SEM model researchers plan to test for the catastrophizing mechanism variable and included steps on how researchers plan to test this model.
26. Updated D6s. Missing Data with strategies to maximize participant compliance and included additional details on addressing missing data via data analysis approach.
27. Updated E4d. Privacy and Confidentiality with procedures on ActiGraph mail ins for data collection and revised an exception to separating all study data from participant identifying information (home practice forms will now be collected via the EMA management system with engagement in home practice data extracted and stored).
28. Updated DSMC Chair from Dr. Alschuler to Dr. Jirikowic.
29. Minor spelling, grammatical, and formatting corrections throughout.
30. Updated page numbers in Table of Contents.

STUDY TEAM ROSTER

Name	Role	Address	Phone/Fax	Email
Mark Jensen, Ph.D.	Principal Investigator	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-543-3185 F: 206-897-4881	mjensen@uw.edu
Melissa Day, Ph.D.	Principal Investigator	330 McElwain Building, Brisbane, AUS 4072	P: 61-7-3365-6421 F: 61-7-3365-4466	m.day@uq.edu.au
Joy Chan, B.S.	Research Coordinator	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-744-3626 F: 206-897-4881	joychan@uw.edu
Sydney Drever, B.A.	Research Study Coordinator	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-616-7671 F: 206-897-4881	drevers@uw.edu
Emily Stensland, B.S.	Research Study Coordinator	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-616-8744 F: 206-897-4881	emilyen@uw.edu
Andrea Thomas, B.S.	Research Study Coordinator	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-221-5688 F: 206-897-4881	pat5@uw.edu
Madison Sherwood, B.A.	Research Assistant	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-616-9242 F: 206-897-4881	msherw7@uw.edu
Shreya Pakalpati, B.A., B.S.	Research Assistant	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-221-5641 F: 206-897-4881	spak97@uw.edu
Nikki Torres, B.S.	Research Assistant	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-616-1750 F: 206-897-4881	ndt77@uw.edu
Emily Goldberg	Research Assistant	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-897-4731 F: 206-897-4881	goldbe@uw.edu
Elena Mendoza, Ph.D.	Study Clinician	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-221-6671 F: 206-897-4881	emendoza@uw.edu
Jennifer Altman, Ph.D.	Study Clinician	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-221-6671 F: 206-897-4881	jka44@uw.edu
Kala Phillips, Ph.D.	Study Clinician	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-616-8205 F: 206-897-4881	kphill@uw.edu
Andrea Newman, Ph.D.	Study Clinician	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-616-8205 F: 206-897-4881	anewman3@uw.edu
Calia Morais, Ph.D.	Study Clinician	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-616-8205 F: 206-897-4881	cmorais@uw.edu
Dawn Ehde, Ph.D.	Co-Investigator	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-744-2811 F: 206-897-4881	ehde@uw.edu
Janna Friedly, M.D.	Co-Investigator	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-744-3026 F: 206-897-4881	friedlyj@uw.edu
Marcia Ciol,	Co-	1959 NE Pacific Street,	P: 206-221-4668	marciac@uw.edu

Ph.D.	Investigator	Box 356490 Seattle WA 98104	F: 206-685-3244	
John Burns, Ph.D.	Co-Investigator	1653 W Congress Pkwy 0 Annex Chicago, IL 60612	P: 312-942-3354 F: 312-942-2874	john_burns@rush.edu
Jeff Borckardt, Ph.D.	Co-Investigator	67 President Street Room 507N Charleston, SC 29425	P: 843-792-3295 F: 843-792-5702	borckard@musc.edu
Beverly Thorn, Ph.D.	Consultant	348 Gordon Palmer Hall 505 Hackberry Lane Tuscaloosa, AL 35487	P: 205-348-5083 F: 205-348-8648	bthorn@ua.edu
Erica Wasmund	Research Study Coordinator	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-897-6322 F: 206-897-4881	ericaw8@uw.edu
Laurel Peabody	Research Study Coordinator	908 Jefferson Street, Box 359612 Seattle WA 98104	P: 206-744-3607 F: 206-897-4881	lpeabody@uw.edu

PARTICIPATING STUDY SITES

Name	Role	Address	Phone/Fax	Email
Mark Jensen, Ph.D.	Principal Investigator	908 Jefferson Street, Box 359612 Seattle, WA 98104	P: 206-543-3185 F: 206-897-4881	mjensen@uw.edu

PRÉCIS

Study Title: Mechanisms of Psychosocial Treatments for Chronic Pain

Objectives

The purpose of this randomized controlled trial is to evaluate the mechanisms of cognitive therapy (CT), mindfulness meditation (MM), and activation skills (AS) as treatments for individuals with chronic pain who endorse low back pain as a primary or secondary pain problem. Participants (240 individuals) will be randomly assigned to eight (8), 1.5 hour telehealth group sessions of (1) CT, (2) MM, or (3) AS. Mechanisms and outcomes will be assessed twice daily during 2-week baseline, 4-week treatment period, and 4-week post-treatment epoch via cue-elicited ecological momentary assessment (EMA); activity level will be monitored during these time epochs via daily monitoring with ActiGraph technology. Follow-up macro-level assessments will be conducted at 3- and 6-months post-treatment. The study will address two aims.

Primary Objective: The objective of the proposed research is to examine the mechanisms of cognitive therapy (CT), mindfulness meditation training (MM), and activation skills treatment (AS) [**Aim 1; Primary**]. After ensuring that there is at least a small effect of time on early treatment changes in the three mechanism variables, we will determine the extent to which late-treatment improvement in primary outcome (pain interference) associated with CT, MM, and AS is predicted by early-treatment changes in cognitive content (i.e., pain catastrophizing), cognitive process (i.e., non-judgment), and/or activity level (i.e., ActiGraph "activity counts").

Hypothesis 1a: Early treatment changes in pain catastrophizing, non-judgment, and activity counts are significantly associated with late treatment improvements in pain interference.

Hypothesis 1b: The Shared Mechanisms Model hypothesizes that if changes in cognitive content, cognitive process, and activity levels are shared mechanisms across the three treatments, then treatment condition will have small and non-significant effects on early changes in the mechanism variables (i.e., the effects of the three treatments on the three mechanism variables will be similar; Shared Mechanisms Model).

Hypothesis 1c: The Specific Mechanisms Model hypothesizes that if changes in content, process, and activity level are mechanisms *specific* to CT, MM, and AS, respectively, then treatment condition will have a significant effect on early changes in the mechanism variables (i.e., the effects of the three treatments on the three mechanism variables will be different, with CT having the largest effects on early treatment decreases in catastrophizing, MM having the largest effects on early treatment increases in non-judgment, and AS having the largest effects on early treatment increases in activity level). Further, later improvement in the primary outcome will be predicted by different mechanism variables as a function of treatment condition; that is, late treatment changes in pain interference will be substantially and uniquely predicted by early treatment changes in: (1) cognitive content (i.e., pain catastrophizing) in CT but not in MM or AS; (2) cognitive process (i.e., non-judgment) in MM but not in CT or AS; and (3) activity level in AS but not in CT or MM, in addition to each mechanism variable significantly predicting the primary outcome (Specific Mechanisms Model).

We also predict that change in the mechanism variables will precede and predict change in outcome, but not vice versa.

Secondary Objective: As a secondary aim, this study will also evaluate the post-treatment mechanisms that explain relapse, maintenance, and continued gains associated with these treatments [**Aim 2; Secondary**]. The Shared (Hypothesis 2a) and Specific (Hypothesis 2b) Mechanism models will also be applied to data collected via EMA and ActiGraph daily during the 4-weeks post-treatment to better understand the post-treatment mechanisms that underlie maintenance of gains and relapse.

Exploratory Objective: Test the Limit, Activate, and Enhance (LAE) moderation model. Specifically, to test if (1) higher baseline levels of catastrophizing are associated with a positive response to the CT intervention, (2) lower baseline levels of activity are associated with a positive response to AS, and (3) higher baseline levels of non-judgment are associated with a positive response to MM.

Primary and Secondary Endpoint: The primary endpoint we propose for the primary study aim (Aim 1) is the post-treatment pain interference score, operationalized as an average of pain interference ratings made on the twice-daily diaries during the first four days after treatment (i.e., Days 43-46). The endpoint for the secondary study aim (Aim 2) is the post-treatment score at 28 days follow-up, as operationalized as the average of days 67-70 of pain interference ratings on the diaries.

Design and Outcomes

A randomized, 3-group parallel design, 240-subject clinical trial to test the mechanisms of cognitive therapy, mindfulness meditation, and activation skills on individuals with chronic pain who endorse low back pain as a primary or secondary pain problem.

Interventions and Duration

Participants will be randomly assigned to eight (8) telehealth group sessions of (1) cognitive therapy (CT), (2) mindfulness meditation (MM), or (3) activation skills (AS). Treatment groups will meet, on average, twice per week over the Zoom videoconferencing platform. Each session will last for a duration of about 90 minutes. Proposed mechanisms and outcomes will be assessed twice daily during 2-week baseline, 4-week treatment period, and 4-week post-treatment epoch via cue-elicited ecological momentary assessment (EMA); activity level will be monitored during these time epochs via daily monitoring with ActiGraph technology. Macro-level assessments will be conducted at pre- and post-treatment and at 3- and 6-months post-treatment.

The total time involved in the study (excluding between session skills practice) is approximately 35-40 hours over an 8 to 9-month period.

Sample Size and Population

We plan to enroll 300 participants with moderate to severe chronic pain including low back pain as a primary or secondary pain problem to achieve a sample size of 240 completers, with 80 completers in each of the treatment groups.

Enrolled participants who complete the required baseline components (baseline data and demographic questions, pre-treatment extended assessment period, technology training, re-assessment of pain interference for general activities with a score of ≥3 for the past 3 months, re-assessment of pain consistency with a response of ≥50% of the time in the past 6 months, and a minimum number of EMA surveys during one week of Baseline Monitoring (Days 1-7) will be randomized to one of the three conditions.

A. SPECIFIC AIMS

A1. Problem Statement

Chronic pain is a common and costly condition affecting millions of Americans, and spine pain (including back and neck pain) is the most common chronic pain condition. Although various psychosocial treatments are effective for chronic pain, there is a critical lack of research examining if these treatments work via the mechanisms specified by theory. Three of the most common components of pain treatments are: (1) Cognitive Therapy (CT); (2) Mindfulness Meditation (MM), and (3) Activation Skills (AS). Theoretically, CT targets unhelpful cognitions (cognitive content, i.e., pain catastrophizing), MM targets how patients think (cognitive process, i.e., non-judgmental awareness), and AS targets what people do (i.e., more "well behaviors"). However, we do not know if these techniques are effective via these specific mechanisms, or via shared mechanisms. Knowledge concerning treatment mechanisms is critical for modifying treatments to focus on the mechanisms that have the greatest benefits for the most patients. Further, understanding the mechanisms underlying post-treatment maintenance of gains and relapse will advance capacity to optimize long-term beneficial outcomes.

Actigraphy and ecological momentary assessment (EMA) consisting of multiple daily measures allows for the evaluation of longitudinal mechanism effects. In the context of a clinical trial, use of actigraphy and EMA data could determine the specific lag times of mechanism effects (i.e., how long it takes for a change in a mechanism to influence key outcomes). Thus, utilizing actigraphy and EMA throughout a controlled trial represents an innovative approach to assessing psychosocial pain treatment mechanisms at a micro-level.

A2. Specific Aims and Hypotheses

In the planned trial, 300 individuals with chronic pain including low back pain as a primary or secondary pain problem will be randomly assigned to telehealth-delivered CT, MM, or AS. Mechanisms and outcomes will be assessed with actigraphy and twice daily EMA during baseline, treatment, and for 4-weeks post-treatment. Mechanisms of longer-term maintenance of gains will be evaluated at 3- and 6-month follow-up. Given past research showing equivalent efficacy for active treatments, we expect no significant group level outcome differences between conditions. However, we do expect *individual* variability in treatment response and maintenance of gains that will allow us to examine mechanisms of change. This study will address two aims.

A2a. Primary Aim and Hypotheses

Aim 1: Examine mechanisms of CT, MM, and AS.

The objective of the proposed research is to examine the mechanisms of cognitive therapy (CT), mindfulness meditation training (MM), and activation skills treatment (AS) [**Aim 1; Primary**]. After ensuring that there is at least a small effect of time on early treatment changes in the three mechanism variables, we will determine the extent to which late-treatment improvement in primary outcome (pain interference) associated with CT, MM, and AS is predicted by early-treatment changes in cognitive content (i.e., pain catastrophizing), cognitive process (i.e., non-judgment), and/or activity level (i.e., ActiGraph "activity counts").

Hypothesis 1a: Early treatment changes in pain catastrophizing, non-judgment, and activity counts are significantly associated with late treatment improvements in pain interference.

Hypothesis 1b: The Shared Mechanisms Model hypothesizes that if changes in cognitive content, cognitive process, and activity levels are shared mechanisms across the three treatments, then treatment condition will have small and non-significant effects on early changes in the mechanism variables (i.e., the effects of the three treatments on the three mechanism variables will be similar; Shared Mechanisms Model).

Hypothesis 1c: The Specific Mechanisms Model hypothesizes that if changes in content, process, and activity level are mechanisms specific to CT, MM, and AS, respectively, then treatment condition will have a significant effect on early changes in the mechanism variables (i.e., the effects of the three treatments on the three mechanism variables will be different, with CT having the largest effects on early treatment decreases in catastrophizing, MM having the largest effects on early treatment increases in non-judgment, and AS having the largest effects on early treatment increases in activity level). Further, later improvement in the primary outcome will be predicted by different mechanism variables as a function of treatment condition; that is, late treatment changes in pain interference will be substantially and uniquely predicted by early treatment changes in: (1) cognitive content (i.e., pain catastrophizing) in CT but not in MM or AS; (2) cognitive process (i.e., non-judgment) in MM but not in CT or AS; and (3) activity level in AS but not in CT or MM, in addition to each mechanism variable significantly predicting the primary outcome (Specific Mechanisms Model).

We also predict that change in the mechanism variables will precede and predict change in outcome, but not vice versa.

A2b. Secondary Aim and Hypotheses

Aim 2: Evaluate the post-treatment mechanisms that explain relapse, maintenance, and continued gains.

As a secondary aim, this study will also evaluate the post-treatment mechanisms that explain relapse, maintenance, and continued gains associated with these treatments [**Aim 2; Secondary**]. The Shared (Hypothesis 2a) and Specific (Hypothesis 2b) Mechanisms Models will also be applied to data collected via EMA and ActiGraph daily during the 4-weeks post-treatment to better understand the post-treatment mechanisms that underlie maintenance of gains and relapse.

Hypothesis 2a: Early post-treatment changes (i.e., post-treatment to 2-weeks post-treatment) in cognitive content, cognitive process, and activity level will be significantly associated with late post-treatment changes (i.e., 2-weeks post-treatment to 4-weeks post-treatment) in pain interference.

Hypothesis 2b: The Shared Mechanisms Model hypothesizes that if early post-treatment changes in cognitive content, cognitive process, and activity levels are shared maintenance mechanisms across the three treatments, then treatment condition will have small and non-significant effects on early post-treatment changes in the mechanism variables (i.e., the effects of the three treatments on the three mechanism variables early post-treatment will be similar; Shared Mechanisms Model).

Hypothesis 2c: The Specific Mechanisms Model hypothesizes that if early post-treatment changes in content, process, and activity level are maintenance mechanisms specific to CT, MM, and AS, respectively, then treatment condition will have a significant effect on early post-treatment changes in the mechanism variables (i.e., the effects of the three treatments on the three mechanism variables early post-treatment will be different, with CT having the largest effects on early post-treatment decreases in catastrophizing, MM having the largest effects on early post-treatment increases in non-judgment, and AS having the largest effects on early post-treatment increases in activity level; Specific Mechanisms Model).

A2c. Exploratory Moderation Aims and Hypotheses

With respect to our moderation model, we based our Limit, Activate, and Enhance (LAE) moderation model on the fact that psychosocial pain treatments can be classified with respect to the extent that they are designed to (1) encourage individauls with chronic pain to reduce or *limit* their use of maladaptive coping responses; (2) teach or encourage individuals with chronic pain to increase or *activate* their use of adaptive coping responses; and (3) build on or *enhance* their signature strengths. The proposed study allows for direct exploration of the utility of the LAE moderation model, along with other exploratory moderators (i.e., patient expectations). Specifically, based on the model, we hypothesize that:

Moderation Hypothesis 1: Baseline levels of catastrophizing will be associated with response to the CT intervention, such that among those participants assigned to the CT intervention, individuals higher in catastrophizing scores at baseline will be more likely to evidence pre- to post-treatment decreases in pain interference than those individuals scoring lower in catastrophizing at baseline. This positive association between baseline catastrophizing and response to CT treatment will be stronger than the association between baseline catastrophizing and response to either the MM or AS treatments (although we would anticipate that all three associations will be positive, because MM and AS treatments are hypothesized to have an indirect effect on catastrophizing, consistent with the Shared Mechanisms Model).

Moderation Hypothesis 2: Baseline activity levels will be negatively associated with response to the AS intervention, such that among those participants assigned to the AS intervention, individuals lower in activity levels will be more likely to evidence pre- to post-treatment decreases in pain interference than those individuals evidencing higher activity levels at baseline. This negative association between baseline activity level and response to AS treatment will be stronger than the association between baseline activity level and response to either CT or MM treatments (although we would anticipate that all three associations will be negative, because CT and MM treatments will have an indirect effect on activity level, consistent with the Shared Mechanisms Model).

Moderation Hypothesis 3: Baseline levels of non-judgment will be associated with response to the MM intervention, such that those participants assigned to the MM intervention who score higher in baseline non-judgmental awareness will be more likely to evidence pre- to post-treatment decreases in pain interference than those individuals evidencing lower levels of non-judgment at baseline.This positive association between the baseline level of non-judgmental awareness and response to MM treatment will be stronger than the association between baseline non-judgmental awareness and response to either AS or CT treatments (although we would anticipate that all three associations will be

positive, because AS and CT treatments will have an indirect effect on non-judgmental awareness, consistent with the Shared Mechanisms Model).

A2d. Additional Exploratory Tests

The collection and analysis of ActiGraph and EMA data will be used to examine the time course of change in cognitive content, cognitive process, and activity level both during treatment (Aim 1) and post-treatment (Aim 2) to determine when mediated changes start to occur, when benefits plateau (or reverse), the time it takes for lag effects to occur, and whether the time course of changes in mediators to outcomes is treatment specific or shared across treatments. In relation to Aims 1 and 2, we will also explore: (1) the effects on, and mechanisms of, change for secondary outcomes (e.g., pain intensity, mood); (2) the role of non-specific mechanisms (e.g., therapeutic alliance).

B. BACKGROUND AND SIGNIFICANCE

B1. Significance of Research

B.1.1. Chronic pain is a serious problem with far reaching implications. Chronic pain is a debilitating, pervasive, and costly problem in the U.S. Previous research has estimated that at a given point in time approximately 30.7% of the U.S. population is experiencing a chronic pain condition that has lasted at least 6 months.[1] This figure translates into an annual cost of approximately $560 to $635 billion per year in direct healthcare expenses, disability compensation, and lost productivity due to chronic pain.[2] There is no way as yet to permanently ameliorate chronic pain, and many of the available biomedical approaches entail potentially serious side effects (e.g., opioid addiction, sedation).[3] Thus, there continues to be an urgent need to develop and evaluate treatments that could improve pain coping and self-management skills for individuals with chronic pain.

B.1.2. Psychosocial interventions for chronic pain are viable treatments that entail few, if any, deleterious side effects. Research has demonstrated that Cognitive-Behavioral Therapy (CBT) and Mindfulness-Based Interventions are efficacious for chronic pain management.[4,5,6] Within these integrated protocols, three specific skills commonly taught are: (1) Cognitive Therapy (CT); (2) Activation skills (AS); and (3) Mindfulness Meditation (MM).[7,8] CT teaches patients to notice thought content and its influences on pain and function. Patients learn to change unhelpful thoughts to make them more realistic and adaptive.[7] AS targets reductions in maladaptive pain behaviors (i.e., pain contingent resting) and uses reinforcement principles to increase well behaviors in the form of engagement in pleasant and valued activities.[9] In contrast, MM encourages patients to disengage from automatic thinking and to mindfully place attention on bodily sensations and other perceptive experiences (e.g., sounds) with a sense of non-judgmental acceptance.[10] While CT, AS, and MM are key components within integrated CBT and Mindfulness-Based Intervention protocols, the relative importance of these specific pain coping skills is not known. A trial of CT vs. AS vs. MM is needed to confirm that each one of these three skills is important for pain management.

B.1.3. Understanding treatment mechanisms is also critical to the advancement of psychosocial pain management. Understanding the mechanisms of psychosocial pain treatments has been identified as a critical next step in our field.[11,12] While equivalent efficacy is typically obtained *on average* when active treatments are compared,[e.g.,13,14] the theories underlying specific treatments argue that effects of different treatments are wrought via unique mechanisms. Testing the mechanisms of different pain treatments could lead to streamlined interventions that distill the most critical change factors into an efficient and cost-effective treatment package. Further, identification of treatment mechanisms will bring order and parsimony to psychotherapeutic theory.[15] Kazdin argues for the importance of testing multiple theory-driven process variables in mechanism research.[16] To determine if mechanisms are unique to a specific treatment or are shared, trans-therapy mechanisms, it is necessary to examine more than one treatment in a mechanism study.

B.1.4. Identifying the mechanisms underlying post-treatment continued improvement, maintenance or loss of treatment gains will inform development of relapse prevention

models. The CT, MM, and AS approaches are designed to be empowering interventions that teach specific skills that patients can continue to use to manage pain long after completion of treatment. However, research underscores the problem of relapse following psychosocial pain interventions.[17] It has been assumed that post-treatment variability in maintenance trajectories depends at least in part on the maintenance of coping skills practice. Based on this assumption, innovative approaches to enhancing skills practice have been applied, with some, albeit limited, beneficial effects.[18,19] The less than optimal efficacy of these relapse prevention interventions may stem from a lack of understanding of the mechanisms of post-treatment improvement, maintenance and relapse.

Research has shown that in as little as one month following treatment many patients experience declines in treatment gains.[20] Research that has examined longer-term outcomes (i.e., 3-, 6-, or 12-month post treatment) is not able to evaluate changes in outcome mediators during this critical period immediately after treatment. One important study comparing CBT to treatment as usual that examined a 2-week post-treatment epoch identified that on average, continued use of active cognitive and behavioral coping, positive affect, self-efficacy and perceived control over pain was associated with maintenance of gains, and pain catastrophizing and negative affect were associated with loss of gains.[21] However, this study did not examine the importance of these treatment maintenance mechanism variables across different treatments, as only one treatment (CBT) was evaluated. Moreover, this study did not evaluate the mechanisms that may be critical beyond a 2-week time frame.[21] To identify at-risk individuals and to inform relapse-prevention models, it is necessary to examine preceding improvement, maintenance, and relapse mechanisms in the one month immediately post-treatment, and to investigate how these factors may relate to longer-term (i.e., 3- and 6-month) follow-up periods.

B.1.5. Selecting the mechanisms to study should be grounded in theory. Various psychosocial treatments have different theoretical bases that propose unique cognitive, behavioral, and emotional therapeutic processes from which treatment-specific mechanisms are derived. In regards to the treatment-specific mechanisms of psychosocial therapies (including CT, MM, and AS), Jensen recently proposed a theoretical model that made a distinction between cognitive content (i.e., what patients believe about their pain), cognitive processes (i.e., how patients think about their pain), and behavioral mechanisms (i.e., what people do).[11] Theoretically, CT targets change in maladaptive cognitive content (i.e., pain catastrophizing) and this is purported to be critical to improve pain outcomes.[22] Hence, change in what patients think is theorized to be a mechanism specific to CT. In contrast, MM explicitly targets change in cognitive processes (i.e., non-judgmental awareness), and this is thought to underlie improved pain outcomes. AS is based on operant theory and is designed to target what patients do in response to pain, specifically to extinguish maladaptive pain behaviors, and to reinforce engagement in goal-directed well behaviors. However, minimal research has examined whether these treatments engender benefit via these specific theorized pathways – the Specific Mechanisms Model – or if benefit is obtained via an amalgamation of shared pathways – the Shared Mechanisms Model. Thus, the question as to whether it is more important to target change in cognitive content, cognitive processes, or behavior, or equally important to focus on all three of these factors, is not yet known.

Tentative support for CT theory exists with several investigations of correlations among pre- to post-treatment change scores finding that improvements in cognitive content variables such as pain catastrophizing,[e.g.,23-26] pain control beliefs,[20-24,25,27] pain helplessness,[28] and other pain-related beliefs[23] are associated with improved outcomes. Further, prospective macro-level (i.e.,

effects tested over weeks) mechanism research investigating how pre- to mid-treatment changes predict subsequent mid- to post-treatment findings using cross-lagged analyses is promising. Two studies using this approach found that early-treatment reductions in pain catastrophizing and helplessness predict late-treatment improvements in pain-related outcomes during an interdisciplinary treatment that included CT.[29,30] While past research is consistent with the potential causal role of cognitive content on functioning, the extent to which cognitions may play such a role in CT specifically has not yet been adequately examined. Scarce research has investigated the mechanisms of MM and AS. The potential mechanism role of mindfulness interventions for pain has been explored in two studies that have found pre- to post-treatment increases in mindfulness correlate with pre- to post-treatment improvement in pain outcomes.[31,32] Although not a mechanism study of AS per se, Redondo and colleagues found that physical activity factors improved among fibromyalgia patients in a physical exercise-based treatment but not in CBT.[33]

A trial currently under way (Burns, PI) will break new ground in implementing macro-level lagged analyses to investigate the mechanisms of CT, Behavioral Therapy, and a mindfulness intervention. However, while this study will evaluate the Specific vs. Shared Mechanisms Model of these treatments at a macro level (i.e., over the course of weeks), it is possible that some of the mechanism effects occur over the course of days (micro- level) and not weeks; it may not take weeks for the beneficial effects of changes in catastrophizing, activity level, or mindfulness to exert beneficial effects. If so, such effects will go undetected in the Burns et al. study. Examination of these micro-level effects is necessary to gain a complete understanding of mechanisms, and to ensure that any treatment modifications are based on a thorough and accurate conceptualization. Understanding these micro-level effects is a focus – and a critical innovative piece – of this trial.

Non-specific mechanisms not theoretically linked to CT, MM or AS are also likely to influence treatment trajectories and outcomes. Psychotherapy research has long maintained that non-specific treatment factors (e.g., therapeutic alliance) should contribute to treatment gains and be non-specific mediator mechanisms shared across different effective interventions. Research across a range of studies and population types has repeatedly shown that alliance, patient expectations and motivation contribute to outcome.[34,35] However, how such factors may function as a foundation for, or facilitator of, specific mediation effects is not well established.

B.1.6. Use of frequent assessments to evaluate treatment mechanisms is needed. To establish that a putative mechanism is a causative factor in determining outcomes, frequent measures are needed.[36] Actigraphy and ecological momentary assessment (EMA) are repeated measures methodologies ideally suited to assess phenomena in real-time.[37] Actigraphy and EMA consisting of multiple daily assessments embedded within an RCT has the capacity to more accurately ascertain mechanism effects, both during treatment and in the critical period immediately post-treatment. EMA has been used in headache trials to examine efficacy.[e.g.,38- 40] However, within non-headache trials, only one study has used EMA for 1-week at pre- and 2-weeks at post-treatment to investigate mechanisms.[21] Importantly, actigraphy and EMA allows for determination of the critical mass of necessary accumulative change in mechanism over days and potentially weeks in order for later, substantive gains (or deterioration) in outcome to occur. This information has important clinical implications: If early change in specific, theoretically derived mechanisms is essential for improved outcome in a given treatment, this suggests that if patients are not obtaining such gains by a critical period, an alternative treatment should be implemented. Further, if a critical reversal in change in a mechanism in the immediate post-treatment epoch is responsible for later relapse at traditional follow-up periods

of 3- and 6-months, then this has important implications for longer-term relapse prevention and maintenance of gains strategies.

C. PRELIMINARY STUDIES

As a group (and often in collaboration), our team has been involved in the design, conduct, and dissemination of ≥30 trials examining the efficacy and mechanisms of pain treatments, including telehealth interventions, and trials within chronic pain populations.[38,41-68] Specifically germane to this trial, we have conducted multiple trials examining CT for chronic back pain and other pain conditions.[24,41,63,69] Results have demonstrated that (1) we have the expertise to conduct the study and (2) we have experience in recruiting and retaining the participants needed for clinical trials.

Expertise in the design, conduct, and dissemination of clinical trials and group-delivered telehealth interventions. Recently we conducted a pilot trial of MBCT for pain compared to a delayed treatment control.[38] The MBCT protocol was feasible, tolerable, and acceptable to participants. Large effects were found for pain interference (***d*** = 1.29), pain intensity, acceptance, and catastrophizing (***d***s = 0.80, 1.22, and .94, respectively). Several team members are currently conducting RCTs that have a MM condition, and one with a CT arm (NIH1R01AT008336; APP1092089). Ehde has completed an RCT comparing a group-based, telehealth-delivered self-management program to a control in adults with spinal cord injury,[68] as well as several other RCTs comparing telehealth interventions for chronic pain and depression management.[70-73] Taken together, Ehde has completed five RCTs that entailed telehealth interventions and assessments, and results have shown this approach is feasible, effective in establishing therapeutic rapport, and results in comparable benefit to that shown via in-person delivery.[42,68,70,72,73]

Process Research. We have published several articles documenting that pre- to post-treatment changes in catastrophizing is a critical mechanism in psychological interventions for pain.[23,24,74] Jensen and colleagues were leaders in emphasizing the need to examine treatment mechanisms and have conducted a number of groundbreaking studies of therapeutic mechanisms embedded in multidisciplinary treatment programs.[23,58,75,76] Burns has also been a pioneer of conducting mechanism research and has examined lagged and cross-lagged associations and showed that early-treatment changes in pain catastrophizing predicted late-treatment outcome changes, whereas early-treatment outcome changes did not predict late-treatment changes in the cognitive factors.[29,30] Recently, Burns and several of the investigators of the current proposal published a paper comparing the Specific and Shared Mechanisms Models (based on *macro*-level assessments) as applied to cognitive and behavioral therapy modules for chronic pain.[77] Burns is currently a PI on a NIH-funded study with several team members that will examine *macro*-level mechanisms of CT, BT, and MBSR and that includes ActiGraph monitoring for assessment of treatment mechanisms. Day and Thorn examined the characteristics of MBCT for pain treatment responders and non-responders (on pain interference and intensity).[78] Findings indicated a medium effect size difference in pain catastrophizing (***d*** = .54) and acceptance (***d*** =.64), suggesting these factors may be critical to the efficacy of MM for pain. Borckardt has published several studies using advanced time-series modeling techniques (i.e., SMA, MLM) to examine mechanistic factors associated with process change in clinical trials in the areas of pain and depression.[79-85] Overall, our mechanism findings indicate that cognitive changes wrought through CT and Mindfulness-Based Interventions are at least correlated with improvement in pain and functioning during psychological interventions for chronic pain.

Ecological Momentary Assessment (EMA) Studies. Our MBCT study[43] (described above) utilized a web-based interface (accessible via smart phone, tablet, laptop, or desktop) to assess pain outcomes, analgesic use, and amount of MM practice on a daily basis both at baseline and

during treatment. Rate of adherence for this EMA methodology was 86% of daily diaries completed by participants (completer sample) across 8-weeks of data collection.[38] Ehde has conducted a 5-week group-based, in-person CBT trial that used daily diary methodology (collected by telephone and paper) within chronic pain populations and that assessed both pain outcomes and proposed cognitive content mediators (pain catastrophizing). Adherence to the daily diary methodology was also high; 88% completed the daily diaries. Publication of these results is in progress (NIH P01HD33988). Dr. Borckardt has successfully conducted multiple EMA-based studies and has expertise in time-series and MLM data analytic techniques in the context of clinical and experimental pain research.[80-82,85-91]

Recruitment of patients with chronic back pain into clinical trials. Members of our research team have developed considerable expertise in recruiting patients with chronic back pain into RCTs, including telehealth-based RCTs. At the sites proposed for inclusion in the present proposal – the University of Washington Medical Center (UWMC) and Harborview Medical Center (HMC) – we have in place proven recruitment and retention methodologies. For a current RCT, we requested a UWMC coding list of patients with a primary or secondary diagnosis code of CLBP that have received services in a 2-year time period; the list we received included approximately 7,500 unique participants. In terms of recruitment success with this population, in a recent CLBP cross-sectional study we conducted we sent approach letters to 1,132 UWMC patients with a CLBP diagnostic code and enrolled 102 participants (9%). In a recently completed multi-site, CLBP RCT (Friedly, PI), the recruitment goal of N = 400 was met over 3 years, with 90% of patients recruited in Year 1.[66] Retention rates in recently completed RCTs conducted by our group range from approximately 85%[92] to 97%[66] of those enrolled (including a telehealth-delivered RCT with a retention rate of 91%), with an average retention rate of 88%. These studies are pertinent to this trial as they entailed similar participant burdens (including daily diary assessments) and recruitment challenges, and we recruited primarily from the University of Washington Medicine system, which is similar to the present proposal. Assuming recruitment will take place over a span of 3.5 years, we can anticipate receiving UWMC coding lists totaling 18,000 unique patients (7,500 patients seen two years prior to the onset of recruitment, approximately 3,000 new unique patients per year for 3.5 years). Based on this information and experience, we estimate that we would deem about 50% or 9,000 patients initially eligible based on study criteria for recruitment into the proposed study. Even if enrollment rate was as low as 5% (of those eligible) and retention rate as low as 80% (which is less than the lowest end of the range we have achieved in previous RCTs, i.e., 85%), we could potentially enroll up to nearly 450 participants, and retain as many as 360 of these in the trial from this recruitment source alone. Thus, even with a highly conservative enrollment and retention rate estimate, these numbers still far exceed those needed for the current study (300 recruited, 240 retained). Further, because the interventions are to be delivered via telehealth, we will have the capacity for recruitment nationwide, if needed; our investigative team has successfully recruited participants into past telehealth trials nationwide via partnering with national consumer organizations (e.g., the National Multiple Sclerosis Society).

D. RESEARCH DESIGN AND METHODS

D1. Synopsis

The sample will include up to 300 adult participants with chronic pain, including low back pain as a primary or secondary pain problem. Study inclusion criteria include: (1) age ≥18 years; (2) endorse having low back pain as a primary or secondary pain problem in the past 6 months; (3) meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in the past 6 months)[1]; (4) average intensity of chronic pain ≥3 on a 10-point scale for most days of the previous 3 months; (5) chronic pain interference for general activities ≥3 on a 10-point scale for the past 3 months; (6) able to read, speak, and understand English to comprehend the worksheets, measures, and interventions implemented; (7) if currently taking analgesic or psychotropic medication, medications must have been stabilized for ≥4 weeks prior to this study; and (8) availability of a telephone, webcam, and microphone through computer or telephone, as well as daily internet access.

Exclusion criteria include: (1) primary pain condition is headache; (2) severe cognitive impairment; (3) current alcohol or substance dependence; (4) active malignancy (e.g., cancer not in remission), terminal illnesses, or serious medical conditions that may interfere with either study participation or with receiving potential treatment benefits (e.g., severe lupus); (5) inability to walk (defined as unable to walk at least 50 yards), which would limit the ability of participants to benefit from the activation skills intervention; (6) significant pain from a recent surgery or injury; (7) pain condition for which surgery has been recommended and is planned; (8) any planned surgery, procedure, or hospitalization that may conflict with or otherwise influence participation in the study; (9) currently receiving or had received other psychosocial treatments for any pain condition (as this may influence these treatment results); (10) current or past participation in a research study with treatment components that may overlap those in the current study; (11) current or history of diagnosis of primary psychotic or major thought disorder within the past 5 years; (12) psychiatric hospitalization within the past 6 months; (13) psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months; (14) any psychiatric or behavioral issues as noted in the medical record or disclosed/observed during self-report screening that would indicate participant may be inappropriate in a group setting; and (15) presenting symptoms at the time of screening that would interfere with participation, specifically active suicidal or homicidal ideation with intent to harm oneself or others, or active delusional or psychotic thinking.

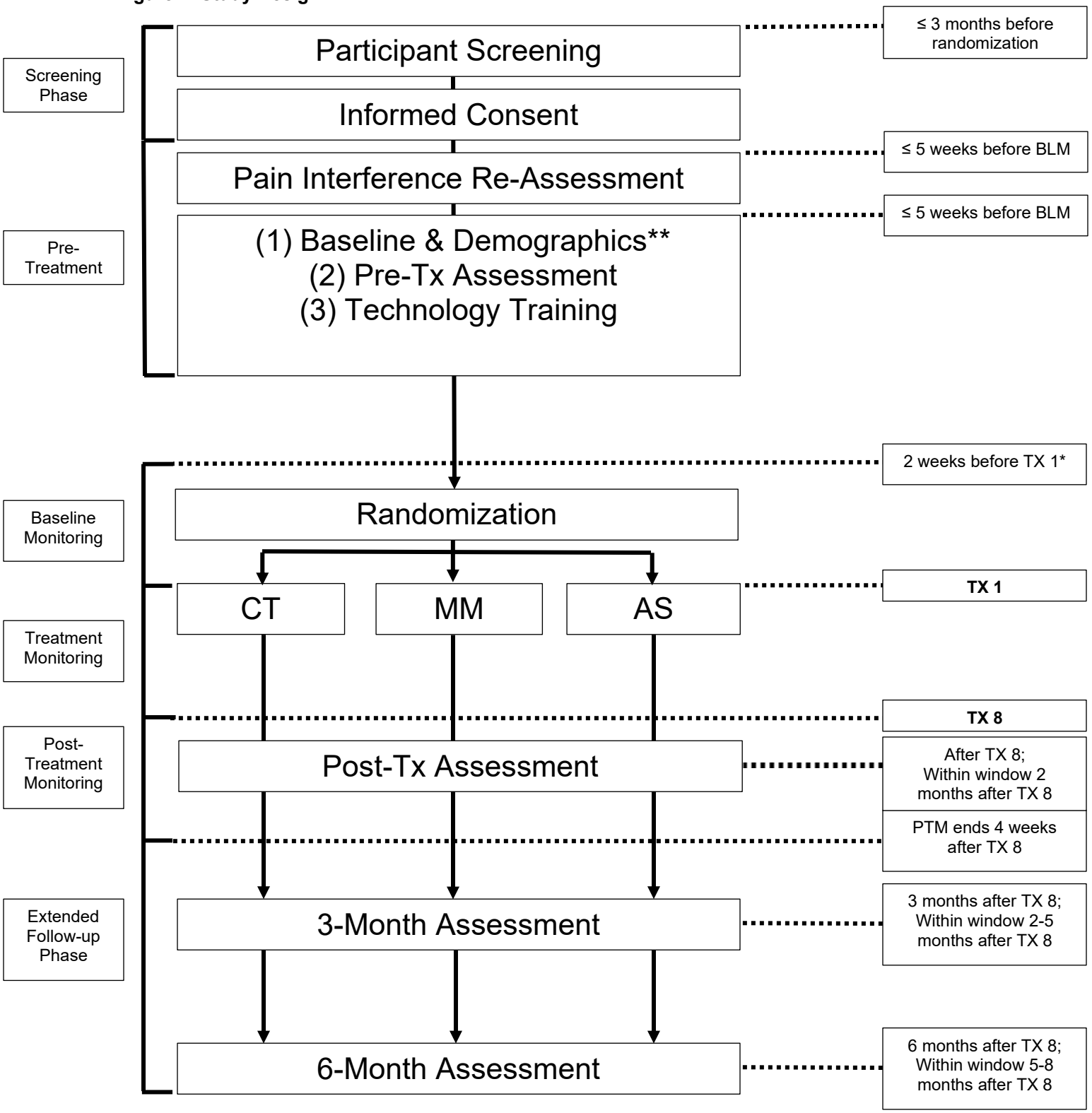
Study participants who meet study inclusion criteria and consent to participate will complete all required baseline components before being randomly assigned to eight, 1.5 hour videoconference-delivered group sessions (2 sessions per week on average) of one of three manualized treatments: (1) cognitive therapy (CT), (2) mindfulness meditation (MM), or (3) behavioral activation skills training (AS). Telephone outcome assessors will be blind to randomization group, and participants will not be told which treatment is expected to be most beneficial. Participants will be told, however, that each of the therapies to which they could be assigned is a type of “pain self-management” intervention that previous patients have found helpful, and that the purpose of the study is to determine how these interventions work.

All measures will be assessed by research staff over telephone at pre- and post-treatment and either by telephone or online at 3-month and 6-month follow-up. We will also invite participants upon completing each assessment period to participate in an optional assessment. Additionally, primary outcome measures and hypothesized mechanism variables will be assessed (via cue-elicited, twice daily EMA methodology accessible via smart phone, tablet,

laptop, and/or desktop) during an approximately 2-week Baseline Monitoring Period, throughout the Treatment Period, and throughout the initial 4-weeks Post-Treatment; activity level will be monitored during these time epochs via daily monitoring with ActiGraph technology. Exploratory moderator variables will be assessed at the initial screening (see Table 1).

The study uses a 3-group parallel design (see Figure 1). During their study participation, all participants will continue to receive their usual medical, psychiatric, and psychotherapeutic care.

Figure 1. Study Design



* Based on the Tx 1 date of the earliest group
** Age, sex, gender, race, and ethnicity data may be collected after informed consent prior to the start of the Pre-Treatment Phase

Table 1. Study Design		
Step	**Data Collected**	**How Often/When**
Pain Interference Re-Assessment	Pain interference, pain consistency, and pain frequency (collected to ensure participant is still eligible for randomization)	Once following consent, before treatment begins
Randomization Stratification	Pain interference (collected to determine randomization stratification)	Once following consent, before treatment begins*
Baseline Data and Demographics	Demographic and general health information, chronic pain history, chronic pain treatment history and surgery history, smoking and alcohol use, CT, MM, and AS treatment history and practice; treatment preference, and pain medication beliefs	Once following consent, before treatment begins
Technology Training	N/A	Once following consent, before treatment begins
Pre-Treatment Assessment	Pain interference, pain catastrophizing, cognitive processes, activity level, average pain intensity, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in pleasurable events, engagement in activities, global quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, perceived cognitive abilities, pain medication beliefs, and COVID-19 effects *Optional Items: Responses to pain, goals, and future expectations*	Once following consent, before treatment begins
2-Week Baseline EMA Monitoring with Actigraphy	EMA: Pain interference, pain catastrophizing, cognitive processes, average pain intensity, mood, pain self-efficacy, sleep/wake time, activity level and activity monitor wear, and treatment credibility and expectancies; Actigraphy: Activity level and sleep	Approximately two weeks before treatment begins; starts two weeks before the date of the earliest treatment group
Randomization	N/A	Once following completion of all Baseline study procedures**
Treatment	Participant engagement as per clinician, amount of home practice per completed home practice documents	Eight sessions, on average twice per week

During Treatment EMA Monitoring with Actigraphy	EMA: Pain interference, pain catastrophizing, cognitive processes, average pain intensity, mood, pain self-efficacy, sleep/wake time, activity level and activity monitor wear, time spent practicing coping skills, therapeutic alliance, group cohesion, and treatment credibility and expectancies; Actigraphy: Activity level and sleep	Begins day of Session 1 and ends day of Session 8
4-Week Post-Treatment EMA Monitoring with Actigraphy	EMA: Pain interference, pain catastrophizing, cognitive processes, average pain intensity, mood, pain self-efficacy, sleep/wake time, activity level and activity monitor wear, and time spent practicing coping skills; Actigraphy: Activity level and sleep	Immediate four weeks following end of treatment
Post-Treatment Assessment	Pain interference, pain catastrophizing, cognitive processes, activity level, average pain intensity, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in pleasurable events, engagement in activities, global quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, perceived cognitive abilities, time spent practicing coping skills, treatment satisfaction, treatment modality, overall participant improvement since beginning treatment, open-ended items about experiences in group and feedback about program, pain medication beliefs, and COVID-19 effects *Optional Items: Responses to pain, goals, and future expectations*	Once following end of treatment; allowable window of up to 2 months after end of treatment
3-Month Assessment	Pain interference, pain catastrophizing, cognitive processes, activity level, average pain intensity, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in pleasurable events, engagement in activities, global quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, perceived cognitive abilities, time spent practicing coping skills, treatment satisfaction, overall participant improvement since beginning treatment, pain medication beliefs, and COVID-19 effects *Optional Items: Responses to pain, goals, and future expectations*	Once three months following end of treatment; allowable window of 2-5 months after end of treatment

6-Month Assessment	Pain interference, pain catastrophizing, cognitive processes, activity level, average pain intensity, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in pleasurable events, engagement in activities, global quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, perceived cognitive abilities, time spent practicing coping skills, treatment satisfaction, overall participant improvement since beginning treatment, pain medication beliefs, and COVID-19 effects *Optional Items: Responses to pain, goals, and future expectations*	Once six months following end of treatment; allowable window of 5-8 months after end of treatment

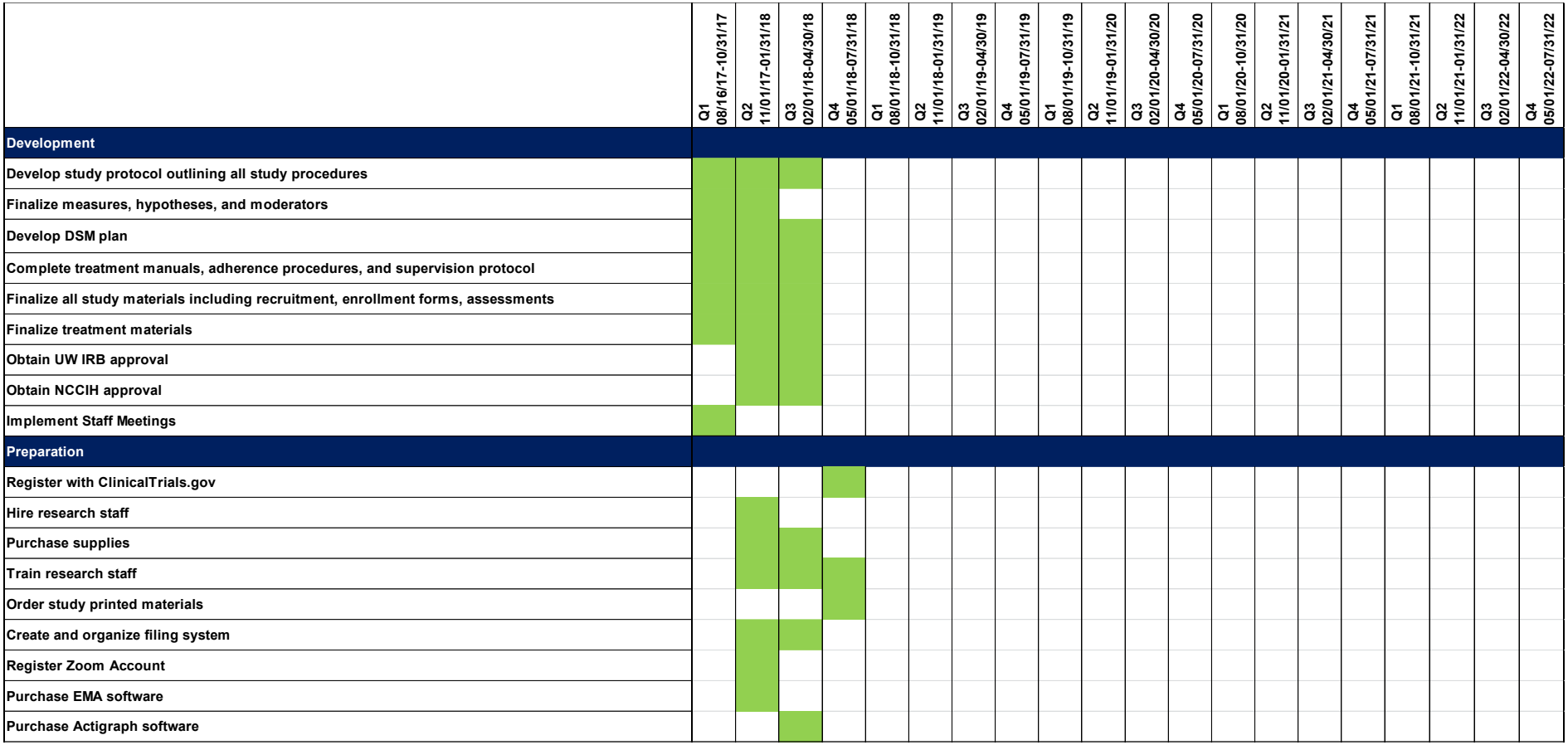
* Will only be administered if participant is still eligible after Pain Interference Re-Assessment

** Only participants who have completed all required baseline study procedures will be randomized. Required procedures include: Baseline Data, Demographics, Pre-Treatment Assessment, Technology Training, Pain Interference Re-Assessment and Randomization Stratification, and completion of a minimum number of EMA surveys.

D2. Study Timeline

We designed a five-year study plan and timeline for achieving short-term study objectives. There will be approximately 42 months available to enroll 300 participants, with 240 participants projected to complete all study elements.

Months 01-12 in Year 01 will be spent hiring staff, finalizing treatment manuals for delivery via Zoom (including adapting workbooks into PowerPoint slides), creating databases, developing and testing the EMA system, and developing internal operating procedures surrounding the study. Participant enrollment will require approximately 3.5 years (42 months; Month 01, Year 02 through Month 06, Year 05). Data collection and cleaning will be ongoing through Month 12, Year 05. Data analysis and dissemination will occur following data collection and cleaning. Drs. Jensen and Day will closely monitor study flow and will hold regular conference calls to coordinate study procedures. Both PIs will be directly involved with the details of the study at every level. Intra-site team meetings with staff and Co-Is will be conducted to ensure any issues will be addressed as they arise.


Q1 08/16/17-10/31/17
Q2 11/01/17-01/31/18
Q3 02/01/18-04/30/18
Q4 05/01/18-07/31/18
Q1 08/01/18-10/31/18
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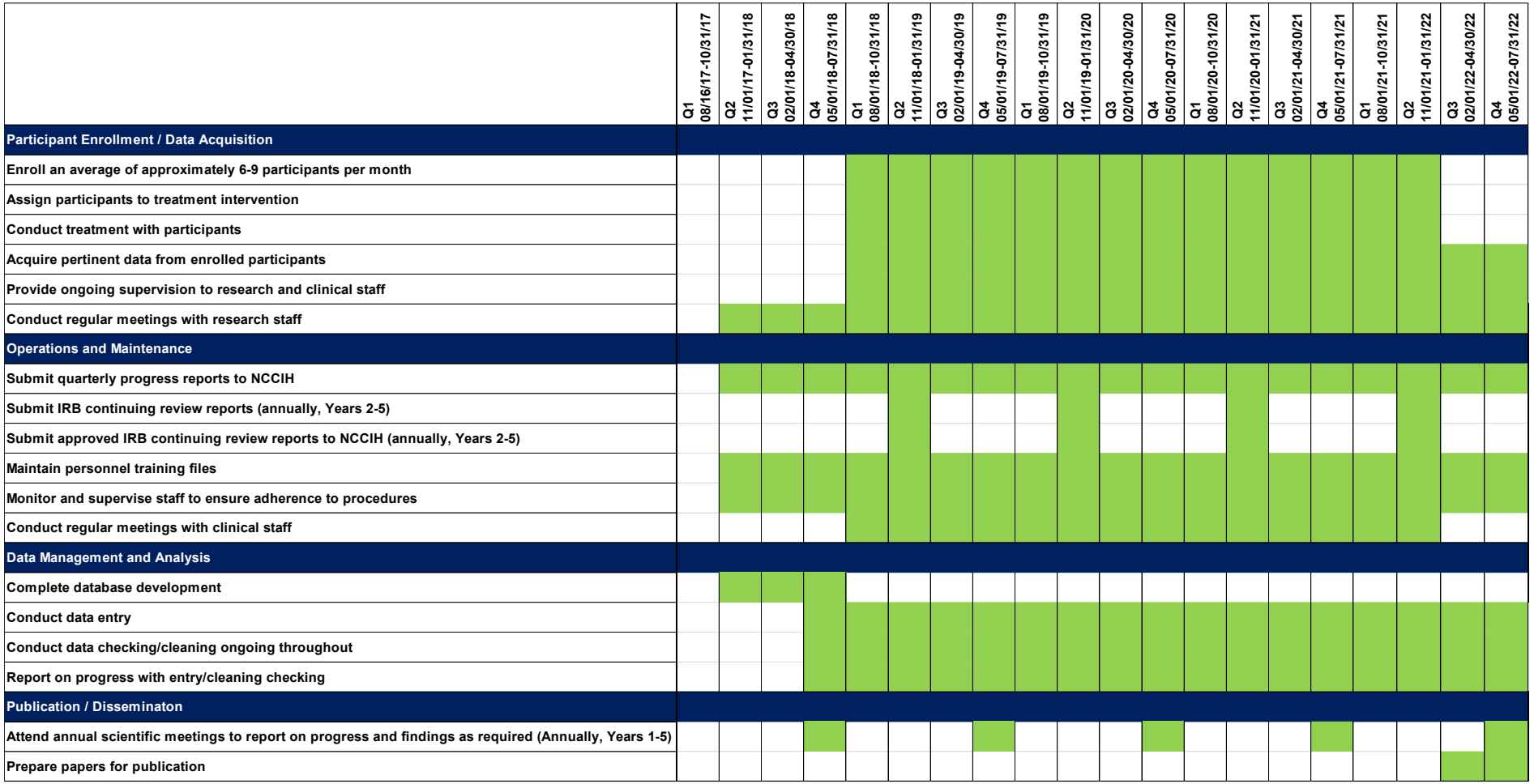
Q3 02/01/21-04/30/21
Q4 05/01/21-07/31/21
Q1 08/01/21-10/31/21
Q2 11/01/21-01/31/22
Q3 02/01/22-04/30/22
Q4 05/01/22-07/31/22
Development
Develop study protocol outlining all study procedures
Finalize measures, hypotheses, and moderators
Develop DSM plan
Complete treatment manuals, adherence procedures, and supervision protocol
Finalize all study materials including recruitment, enrollment forms, assessments
Finalize treatment materials
Obtain UW IRB approval
Obtain NCCIH approval
Implement Staff Meetings
Preparation
Register with ClinicalTrials.gov
Hire research staff
Purchase supplies
Train research staff
Order study printed materials
Create and organize filing system
Register Zoom Account
Purchase EMA software
Purchase Actigraph software


Q1 08/16/17-10/31/17
Q2 11/01/17-01/31/18
Q3 02/01/18-04/30/18
Q4 05/01/18-07/31/18
Q1 08/01/18-10/31/18
Q2 11/01/18-01/31/19
Q3 02/01/19-04/30/19
Q4 05/01/19-07/31/19
Q1 08/01/19-10/31/19
Q2 11/01/19-01/31/20
Q3 02/01/20-04/30/20
Q4 05/01/20-07/31/20
Q1 08/01/20-10/31/20
Q2 11/01/20-01/31/21
Q3 02/01/21-04/30/21
Q4 05/01/21-07/31/21
Q1 08/01/21-10/31/21
Q2 11/01/21-01/31/22
Q3 02/01/22-04/30/22
Q4 05/01/22-07/31/22
Participant Enrollment / Data Acquisition
Enroll an average of approximately 6-9 participants per month
Assign participants to treatment intervention
Conduct treatment with participants
Acquire pertinent data from enrolled participants
Provide ongoing supervision to research and clinical staff
Conduct regular meetings with research staff
Operations and Maintenance
Submit quarterly progress reports to NCCIH
Submit IRB continuing review reports (annually, Years 2-5)
Submit approved IRB continuing review reports to NCCIH (annually, Years 2-5)
Maintain personnel training files
Monitor and supervise staff to ensure adherence to procedures
Conduct regular meetings with clinical staff
Data Management and Analysis
Complete database development
Conduct data entry
Conduct data checking/cleaning ongoing throughout
Report on progress with entry/cleaning checking
Publication / Disseminaton
Attend annual scientific meetings to report on progress and findings as required (Annually, Years 1-5)
Prepare papers for publication

D3. Inter-Site Communication and Coordination

Routine communication and coordination between the investigators will occur primarily through joint teleconferenced executive meetings. The PIs will communicate bi-weekly (scheduled) or more often (if needed), either by phone, e-mail, or Skype/Zoom, as well as in-person 1-2 times per each year of the funded period, to discuss experimental design, data analysis, and all administrative responsibilities. They will work in close collaboration with the study investigators to discuss the direction of the research project and the reprogramming of funds, if necessary. Scheduled project wide meetings with all study investigators and study staff will be held on a monthly basis and will be chaired by Dr. Day; Dr. Day and other investigators not located on the University of Washington campus will primarily be present via Zoom for these meetings, and occasionally in-person and/or via conference call.

D4. Participant Recruitment and Feasibility

Potential participants with chronic pain who also have low back pain will be primarily identified via diagnostic codes in the University of Washington Medical Center (UWMC) / Harborview Medical Center (HMC) medical records. Recruitment approaches could also include several other modalities, if required. These include using our department's research participant pool and reaching out to past participants who indicated interest in contact about future studies, posting flyers and brochures in relevant clinics, such as Spine and Rehabilitation Medicine clinics at both HMC and UWMC; and announcements about the study on the hospital-wide electronic reader board and through the UW Medicine Newsroom (https://newsroom.uw.edu/), which publicizes studies that are enrolling participants through a variety of electronic, print, and social media sources. The pool of potential participants currently includes about 9,000 initially eligible individuals.

Clinicians in UWMC clinics (as well as clinics outside of the UWMC system that agree to participate in recruitment efforts) will be periodically alerted to this study and its eligibility criteria and encouraged to refer patients who meet criteria and for whom this would be clinically appropriate. Identified individuals will be added to a participant registry and will be contacted and sent information that describes the study and invites them to participate. Interested individuals may also be instructed to directly contact study investigators.

Additionally, research staff may pre-screen lists of patients with upcoming appointments in relevant clinics at both HMC and UWMC for potential participants. Participants meeting eligibility criteria will be contacted and sent information that describes the study and invites them to participate. Potential participants may also be approached in clinic about the study.

If needed, we will also recruit nationally. If so, we plan to post the study on ClinicalTrials.gov and we may also use social media sources and ResearchMatch.org if needed and appropriate. In addition, and again if needed, we would plan to seek input from other NCCIH investigators and colleagues regarding ideas for recruiting individuals with chronic pain from national samples.

In addition to these primary recruitment sources, we will also recruit using social media, online forums, websites, patient advisory networks, and other online mediums that are pertinent to chronic pain. We will also encourage providers, participants, and interested individuals to pass along our study information to others as they see fit.

The recruitment sources described above will provide participants who are representative of the general population with a history of chronic pain and enhance the generalizability of the study results.

D5. Participants

We propose to enroll 300 participants in order to ensure complete data from 240 randomized participants, assuming a very conservative 20% drop-out rate (the dropout rate in our other studies has never reached below 15%). We will monitor the dropout rate on an ongoing basis, and modify the number of participants recruited as needed to ensure a final sample of N = 240 study completers.

Eligibility Criteria

Inclusion Criteria:

(1) Age ≥18 years;
(2) Endorse having low back pain as a primary or secondary pain problem in the past 6 months;
(3) Meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in past 6 months);
(4) Average intensity of chronic pain ≥3 on a 10-point scale for most days of the previous 3 months;
(5) Chronic pain interference for general activities ≥3 on a 10-point scale for the past 3 months;
(6) Able to read, speak, and understand English;
(7) If currently taking analgesic or psychotropic medication, medications must have been stabilized for ≥4 weeks prior to this study; and
(8) Availability of a telephone, webcam, and microphone through computer or telephone, as well as daily internet access.

Exclusion Criteria:

(1) Primary pain condition is headache;
(2) Severe cognitive impairment;
(3) Current alcohol or substance dependence;
(4) Active malignancy (e.g., cancer not in remission), terminal illnesses, or serious medical conditions that may interfere with either study participation or with receiving potential treatment benefits (e.g., severe lupus);
(5) Inability to walk (defined as unable to walk at least 50 yards), which would limit the ability of participants to benefit from the activation skills intervention;
(6) Significant pain from a recent surgery or injury;
(7) Pain condition for which surgery has been recommended and is planned;
(8) Any planned surgery, procedure, or hospitalization that may conflict with or otherwise influence participation in the study;
(9) Currently receiving or had received other psychosocial treatments for any pain condition;
(10) Current or past participation in a research study with treatment components that may overlap those in the current study;
(11) Current or history of diagnosis of primary psychotic or major thought disorder within the past 5 years;

(12) Psychiatric hospitalization within the past 6 months;
(13) Psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months;
(14) Any psychiatric or behavioral issues as noted in the medical record or disclosed/observed during self-report screening that would indicate participant may be inappropriate in a group setting; and
(15) Presenting symptoms at the time of screening that would interfere with participation, specifically active suicidal or homicidal ideation with intent to harm oneself or others or active delusional or psychotic thinking.

Clinical discretion may be exercised as needed regarding mental health exclusion criteria above to determine appropriateness in a group setting.

We will not have an upper age cutoff for study participation because we have successfully treated individuals at all ages, including those over 80 years old.

D6. Procedures

D6a. Recruitment

IMPORTANT: All materials and procedures listed below to be used for recruitment will be submitted to the University of Washington IRB for review and approval.

Prospective participants will be identified primarily through select medical record review until this recruitment source no longer becomes viable.

Select Medical Record Review

Researchers will receive lists of patients with a diagnosis of chronic pain who have received services at either the University of Washington Medical Center (UWMC) or Harborview Medical Center (HMC) systems. These lists may contain the patient's contact information and information related to the patient's UWMC/HMC visits. Such information could include, for example, clinics visited, reasons for visits, dates of visits, visit outcomes, diagnoses, problem lists, and medications taken. This information would be used to sort and filter patients to determine preliminary eligibility for this study. Staff may review the medical records of these patients in the UWMC/HMC medical records system for pre-screening purposes to verify a pain problem and confirm study eligibility if the information contained in the list is not sufficient to make a determination. Research staff would send eligible patients an approach letter or email along with an information sheet about the study if s/he is deemed eligible. Patients may also receive an approach text message. The patient would then contact research staff via telephone if interested in participating in the study. Research staff would call patients following the initial contact attempt if there is no response to make sure the patient received the letter. Research staff would use a script to inquire whether the patient is interested in participating in the research study or not. Research staff would initiate the study self-report screening process over the telephone if the patient is interested in participating using the research recruitment script and electronic screening case report form (self-report screening protocol described in detail below).

Number of Contacts: Research staff would send one approach letter or email, and then attempt to reach the patient over the phone. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later

point, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

Other Studies and Research Registries

Research staff may contact participants who participated in previous studies who agreed to be contacted for further research opportunities, or are enrolled in a research registry (such as the department's Participant Pool, or others like it). We may also contact participants who are referred to us by other research studies, or use another study's participant lists/databases (provided by the other study with all IRB permissions in place).

Participants from these sources will be sent an approach letter or email with a FAQ sheet that will explain the study in more detail; participants may also receive an approach text message.

Number of Contacts: Research staff would send one approach letter or email, and then attempt to reach the patient over the phone. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

<u>If needed</u>, we will also recruit from the following sources:

Provider Referral

1) Health care providers from the UWMC/HMC Spine and Rehabilitation Medicine clinics, primary care clinics, and clinics/medical organizations outside of the UWMC/HMC system who agree to participate in recruitment efforts, may also provide research staff members the contact information of potential patients who expressed interest in participating in the research study or the provider deems may be a good fit for the study. Research staff would reach out via email or phone (depending on what contact information is provided) and initiate the study screening process if a patient is interested in participating using the research recruitment script and screening case report form (self-report screening protocol described in detail below).

   Number of Contacts: Research staff may send one approach letter or email, and then attempt to reach the patient over the phone. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

2) Providers can also refer patients to the study by providing the patient with recruitment materials or study contact information and inviting them to follow-up independently. The patient would then contact research staff if interested in participating in the study.

   Number of Contacts: Following initial contact by patient, research staff would then attempt to reach the patient over phone or email. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, research staff may then send a final letter indicating research

staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

3) In addition, medical records may be reviewed for patients with upcoming visits to certain clinics (e.g., various Spine and Rehabilitation Medicine clinics) where we expect a high rate of interest, relevance, and eligibility. Research staff may contact a provider to inform them when a particular patient who appears to be eligible for the study based on the medical record screening protocol will be attending an upcoming appointment, and that staff would like the provider to mention the study to the patient. Ideally this would then result in scenario #1 described above.

4) As needed, research staff will review the medical records of patients who have upcoming appointments at the UWMC or HMC Spine, Rehabilitation Medicine, or other relevant clinics for a chronic pain problem. If s/he is deemed eligible, research staff may send the patient an approach letter or email along with an information sheet about the study prior to their appointment that indicates why they are being approached, and informs them that they may be approached by research staff during their next appointment in the clinic. The patient would then contact research staff if interested in participating in the study. Research staff may approach the patient during their next appointment to see if they would be interested in participating if the patient does not contact the research team. Research staff may also approach patients directly in clinic without first using an approach letter or email if a specific clinic has provided permission for researchers to recruit with this method. Research staff would initiate the study self-report screening process if the patient is interested in participating using the research recruitment script and screening case report form in a private location, or set up a time to conduct the screening over the telephone (self-report screening protocol described in detail below).

Number of Contacts: Research staff may send one approach letter or email and may make one initial, in-person approach in clinic. If the patient indicates interest but does not want to discuss the study in clinic, staff will attempt to reach the patient over the phone. In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

In-Person Recruitment in Clinics and Other Spaces

Research staff may also recruit potential participants via in-person efforts in clinics where permission has been granted by clinic management/leadership or in other spaces as deemed appropriate. For locations where permission is needed to recruit in-person, researchers will seek and receive all approvals before engaging in such activities. Examples of in-person recruitment include, but are not limited to, setting up a table with a research staff member and recruitment materials, engaging waiting individuals or passerbys with recruitment materials (e.g., a brochure) and/or a short pitch about the study, or participating in an event targeting research or participant recruitment (e.g., a research fair). Staff may collect basic contact information such as name, telephone number, and/or email address from in-person recruitment efforts; staff may also schedule a time with the potential participant to follow up with more details and/or start the screening process.

Self-Referral

If needed, flyers and brochures describing the study will be made available throughout clinics where we expect a high rate of interest, relevance, and eligibility. There may also be announcements about the study on the hospital-wide electronic reader board and through the UW Medicine Newsroom (https://newsroom.uw.edu/), which publicizes studies that are enrolling participants through a variety of electronic, print, and social media sources. Interested patients would then contact research staff via telephone or email.

If researchers are interviewed regarding the study, video or audio information about the study may be disseminated by news agencies in addition to any stories that may get published in print or online. Researchers may also place print or electronic advertisements or articles in publications such as newspapers, magazines, or newsletters. Additionally, researchers may take out advertisements in physical spaces such as on transit (e.g., buses, trains, trolleys) or at transit stations. If other viable locations for physical or electronic advertisements arise, researchers will work with the appropriate parties for permission and pricing considerations. All ads will display basic information about the study and study contact information. Interested people will contact the study directly after seeing the ad (or story, if researchers are featured in a news release). Research staff would initiate the study self-report screening process over the telephone if the patient is interested in participating in the study using the research recruitment script and screening case report form (self-report screening protocol described in detail below).

If recruitment is opened up beyond patients in the UWMC/HMC system, potential participants will be able to contact research staff after seeing our listing on ClinicalTrials.gov or on any other websites, forums, blogs, patient advisory networks, and social media sites researchers decide to post the study. Research staff would initiate the study self-report screening process if the patient is interested in participating in the study using the research recruitment script and screening case report form (self-report screening protocol described in detail below).

Number of Contacts: Following initial contact by the potential participant, research staff will attempt to reach the patient over the phone (or email, if contacted via email and participant did not provide a phone number). In instances where a patient seems likely to participate in the study or expresses interest but then becomes unable to contact at a later point, if we have the potential participant's mailing address, research staff may then send a final letter indicating research staff will no longer be attempting to contact the patient unless notified otherwise by the patient before terminating attempts.

ResearchMatch.org

ResearchMatch is a national health volunteer registry that was created by several academic institutions and supported by the U.S. National Institutes of Health as part of the Clinical Translational Science Award (CTSA) program. ResearchMatch has a large population of volunteers who have consented to be contacted by researchers about health studies for which they may be eligible. The database currently contains over 120,000 volunteers across the United States who have created profiles and are ready to be matched to appropriate research studies.

Research staff will search for appropriate matches amongst the non-identifiable ResearchMatch volunteer profiles in the system by entering in as much of the study's inclusion and exclusion criteria into ResearchMatch's Search Builder. The Search Builder will then yield a list of potential matches based on the search criteria. Staff will send out an initial recruitment message to these potential matches through ResearchMatch. The secure ResearchMatch clearinghouse will route the message to each of the potential matches and they will have the

option of replying yes, no, or no response. By replying yes, ResearchMatch releases the volunteer's contact information so that researchers may follow up with the volunteer directly. A volunteer has the option of listing his/her mailing address, telephone number, and/or email address; some volunteers may only list one mode of contact while others may choose to list multiple.

Once the volunteer has authorized ResearchMatch to release their contact information to us, staff will contact the volunteer using his/her provided contact information. There are several possible routes we may contact volunteers, depending on what types of contact information the volunteer provides researchers. A specific approach letter and information sheet will be used when contacted via postal mailing, or a specific approach email when contacted via email. The research recruitment script will be used when contacted via telephone. If the volunteer is interested in being screened for the study, staff will go through the self-report screening process.

The recruitment approaches described above will provide participants who are representative of the general population with chronic pain, and enhance the generalizability of the study results. If needed, we would plan to seek input from other NCCIH investigators and colleagues regarding other ideas for recruiting individuals with chronic pain from national samples.

Research staff will use a combination of postal mail, email, phone, and/or text messaging during study recruitment, depending on recruitment source, participant preference, and/or what seems to be the easiest way to get a hold of the participant. Please note that only research staff members will screen, consent, or perform study procedures with potential participants.

D6b. Screening Procedures

The study screening procedures for participants will consist of the following:

Self-Report Screening

Research staff will ask potential participants a set of formalized IRB-approved questions to determine eligibility based on all of the study inclusion/exclusion criteria listed below with the assistance of the screening case report form.

Self-reported inclusion criteria include the presence of chronic pain, operationalized as follows:

- Meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in the past 6 months);
- Average intensity of chronic pain ≥3 on a 10-point scale for most days of the previous 3 months.

Additional self-report inclusion criteria include:

- Age ≥18 years;
- Endorsement of having low back pain as a primary or secondary pain problem in the past 6 months;
- Able to read, speak, and understand English;
- Chronic pain interference for general activities ≥3 on a 10-point scale for the past 3 months;

- If currently taking analgesic or psychotropic medication, medications must have been stabilized for ≥4 weeks prior to screening;*
- Availability of a telephone, webcam, and microphone through computer, telephone, or other mobile device; as well as daily internet access.

* Research staff will ask potential participants if they have been prescribed any new medications or changed the dosages/frequencies in any of their medications in the past four weeks. If the potential participant reports yes, staff will ask for the medication name and determine if the medication is an analgesic or psychotropic medication. If the medication is an analgesic or psychotropic medication, staff will inform the participant they will call them back at a date four weeks or more since the date of the medication change to check if their medications have stabilized and continue the self-report screening (see re-screening section below).

Self-report exclusion criteria include:

- Primary pain condition is headache;
- Severe cognitive impairment;
- Current alcohol or substance dependence;
- Active malignancy (e.g., cancer not in remission), terminal illnesses, or serious medical conditions that may interfere with either study participation or with receiving potential treatment benefits (e.g., severe lupus);
- Inability to walk (defined as unable to walk at least 50 yards), which would limit the ability of participants to benefit from the activation skills intervention;
- Significant pain from a recent surgery or injury;
- Pain condition for which surgery has been recommended and is planned;
- Any planned surgery, procedure, or hospitalization that may conflict with or otherwise influence participation in the study;
- Currently receiving or had received other psychosocial treatments for any pain condition;
- Current or past participation in a research study with treatment components that may overlap those in the current study.

Self-reported exclusion criteria also include psychiatric or behavioral disorders that would interfere with ability to participate, as operationalized below:

- Current or history of diagnosis of primary psychotic or major thought disorder within the past 5 years;
- Psychiatric hospitalization within the past 6 months;
- Psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months;
- Any psychiatric or behavioral issues disclosed or noticed during self-report screening that would indicate participant may be inappropriate in a group setting;
- Presenting symptoms at the time of screening that would interfere with participation, specifically active suicidal or homicidal ideation with intent to harm oneself or others or active delusional or psychotic thinking.**

Clinical discretion may be exercised as needed regarding mental health exclusion criteria above to determine appropriateness in a group setting.

** If during self-report screening the potential participant presents symptoms of active suicidal ideation, research staff will implement the emergent situations protocol (see section Suicide Risk Assessment Protocol). If there are any questions or concerns regarding the potential participant's psychological, behavioral, or cognitive appropriateness for the study, research staff will either (1) ask the participant if staff may call him/her back at a later time after consulting with a study investigator, or (2) ask for the potential participant's permission to have a licensed psychologist or a Masters-level or post-doctoral level clinician supervised by a licensed psychologist speak with the potential participant.

The psychologist or Masters-level or post-doctoral clinician (supervised by one of the study Co-PIs, Dr. Jensen, who is a licensed clinical psychologist) will use his/her clinical expertise and judgment to ask the potential participant some additional questions to assess the participant for the concerns (e.g., active suicidal or homicidal ideation or active delusional or psychotic thinking) raised by research staff. Clinical discretion may be exercised as needed regarding mental health exclusion criteria. The psychologist or Masters-level or post-doctoral clinician will relay the outcome of the call back to the staff member completing the self-report screening.

Ineligible Participants

Research staff will offer ineligible participants a list of resources with information about treatment of pain (e.g., books, internet resources, etc.) and any relevant clinical resources available. While staff will do their best in offering participants resources, there may be situations where there may not be an opportunity for staff to offer resources, or offering one may be inappropriate, e.g., the participant is hostile, aggressive, or disrespectful and/or terminates the conversation before staff are able to offer resources.

This resource list will also be available to enrolled participants who inquire about additional resources. The resource list will be accompanied with a cover letter if sent via mail.

Potential Participants who Decline

Research staff will collect basic demographic information from all participants who are deemed eligible to participate (following at least self-report screening) yet decline to participate. These data will be collected to determine if there are significant differences between eligible participants who enroll and those who do not.

Re-Screening

Research staff will re-screen eligible participants with the use of a re-screening script on the following mutable inclusion criteria if 3 months or more have elapsed between the initial screening and randomization OR if there is a revision of the screening questions used in determining eligibility. Re-screenings will always be done using the most current approved version of the screening form and will need to be done for participants who have not yet been randomized. The following criteria will be assessed:

1. Meet criteria for having a chronic pain problem (≥3 months, with pain experienced on ≥50% of days in the past 6 months);
2. Average intensity of chronic pain ≥3 on a 10-point scale for most days of the previous 3 months;
3. Chronic pain interference for general activities ≥3 on a 10-point scale for the past 3 months;
4. Endorsement of having low back pain as a primary or secondary pain problem in the past 6 months;

5. If currently taking analgesic or psychotropic medication, medications must have been stabilized for ≥4 weeks prior to this study;*
6. Availability of a telephone, webcam, and microphone through computer, telephone, or other mobile device; as well as daily internet access.

* Research Staff will ask potential participants if they have been prescribed any new medications or changed the dosages/frequencies in any of their medications in the past four weeks. If the potential participant reports yes, staff will ask for the medication name and determine if the medication is an analgesic or psychotropic medication. If the medication is an analgesic or psychotropic medication, staff will inform the participant they will call them back at a date four weeks or more since the date of the medication change to check if their medications have stabilized and continue the self-report screening.

In addition, research staff will re-screen eligible participants on the following mutable exclusion criteria if 3 months or more have elapsed between the initial screening and randomization OR if there is a revision of the screening questions used in determining eligibility:

1. Primary pain condition is headache;
2. Severe cognitive impairment;
3. Current alcohol or substance dependence;
4. Active malignancy (e.g., cancer not in remission), terminal illnesses, or serious medical conditions that may interfere with either study participation or with receiving potential treatment benefits (e.g., severe lupus);
5. Inability to walk (defined as unable to walk at least 50 yards), which would limit the ability of participants to benefit from the activation skills intervention;
6. Significant pain from a recent surgery or injury;
7. Pain condition for which surgery has been recommended and is planned;
8. Any planned surgery, procedure, or hospitalization that may conflict with or otherwise influence participation in the study;
9. Currently receiving or had received other psychosocial treatments for any pain condition;
10. Current or past participation in a research study with treatment components that may overlap those in the current study;
11. Current or history of diagnosis of primary psychotic or major thought disorder within the past 5 years;
12. Psychiatric hospitalization within the past 6 months;
13. Psychiatric or behavioral conditions in which symptoms were unstable or severe within the past 6 months;
14. Any psychiatric or behavioral issues disclosed or noticed during self-report screening that would indicate participant may be inappropriate in a group setting;
15. Presenting symptoms at the time of screening that would interfere with participation, specifically active suicidal or homicidal ideation with intent to harm oneself or others or active delusional or psychotic thinking.**

** If during self-report re-screening the potential participant presents symptoms of active suicidal ideation, research staff will implement the emergent situations protocol (see Suicide Risk Assessment Protocol). If there are any questions or concerns regarding the potential participant's psychological, behavioral, or cognitive appropriateness for the study, research staff will either (1) ask the participant if staff may call him/her back at a later time after consulting with a study investigator, or (2) ask for the potential participant's permission to have a licensed psychologist or a Masters-level or post-doctoral clinician supervised by a licensed psychologist speak with the potential participant.

The psychologist or Masters-level or post-doctoral clinician will use his/her clinical expertise and judgment to ask the potential participant some additional questions to assess the participant for the concerns (e.g., active suicidal ideation or active delusional or psychotic thinking) raised by research staff. Clinical discretion may be exercised as needed regarding mental health exclusion criteria. The psychologist or Masters-level or post-doctoral clinician will relay the outcome of the call back to the staff member completing the self-report screening.

Screening procedures for this study will not require a physical examination or laboratory procedures.

The recruitment outcome for each participant will be captured using an electronic recruitment outcome case report form. The data collected will help ensure accurate reporting of recruitment and enrollment efforts in future publications.

The self-report screening component may take place up to 6 months prior to the randomization for that particular cohort.

D6c. Consent Process

All participants who meet eligibility criteria following all components of the screening procedures will then undergo the informed consent process if they wish to participate. Research staff will participate in and obtain informed consent from research participants after screening but prior to commencement of any further study procedures. The informed consent process will take place over the telephone at a time deemed mutually feasible for the participant and staff member and coordinated on a case-by-case basis.

Prior to the informed consent process, research staff will email (or postal mail, if the participant prefers) a copy of the information statement for the participant to review as well as the date and time of the appointment. Participants will be encouraged to read the information statement prior to the scheduled consent session and to be prepared with any questions. If the informed consent session is scheduled more than two business days in advance, research staff will ask to call, text, and/or email participants as a reminder. Participants will be requested to have the information statement in front of them during the consent session.

A research staff member will review each section of the information statement approved by the UW IRB, inviting discussion to ensure comprehension. Staff will be trained by study investigators to ensure competency to discuss informed consent and strategies to ensure there is no coercion.

Participants will be provided with as much time as needed to review the information statement and ask the research staff member questions about the information statement, their rights as human participants, and participation in the study. Potential participants will be fully informed of all risks and benefits prior to giving their verbal informed consent and prior to enrollment in the study. **Potential participants will also be informed that providing consent for enrollment into the study does not guarantee assignment to a treatment intervention, as this is contingent on completing certain required baseline procedures (see randomization section below).**

If during the course of this contact the potential participant has questions that cannot be addressed by research staff, one of the study investigators or the research coordinator (depending on the nature of the questions) will follow up with the potential participant to answer the questions. Participants may take time to think about participating and render a decision at a subsequent time.

Potential participants will be asked to repeat back to research staff their understanding of the information statement material as necessary. Individuals will not be permitted to participate if there is any question as to whether a person has capacity to provide informed consent.

When all questions have been answered, research staff will ask the participant if they would like to participate in the study. The participant will then be asked to provide verbal consent to participate. The participant will not need to sign the information statement, as we have a Waiver of Documentation of Informed Consent through our institution's IRB.

Research staff may also ask the participant if they would like to learn more information about enrolling into the department's research participant pool. The participant pool consists of individuals who indicated interest in participating in Department of Rehabilitation Medicine research studies and who have agreed to be contacted by researchers for future studies. If the participant is interested in being part of the participant pool, research staff will let the participant know researchers managing the participant pool will be following up separately with him/her to provide more information. Participants may decline to participate in the participant pool and still participate in the research study.

Research staff will provide participants with staff contact information (emailed) after the consent process. Participants will be sent a response key to help answer questions asked during the extended telephone assessments. Staff will also provide the participant with a schedule of the study procedures. If anything is mailed, it will be accompanied by a cover letter.

Research staff will complete an electronic enrollment case report form as well as documenting the consent process form in REDCap for each enrolled participant that will be included with study data. The REDCap system will allow researchers to create an audit trail, as well as capture an e-signature from research staff attesting to the validity of the data entered.

Participants may be screened and enrolled up to 3 months from the date they are randomized to a treatment intervention. However, if a participant is enrolled but more than 3 months will have passed between their date of consent and date they will be randomized, staff will re-screen the participant to ensure s/he is still eligible for the study.

D6d. Baseline Data and Demographic Information

After providing informed consent, research staff will ask the participant to provide demographic data (e.g., age, sex, gender orientation, ethnicity/race, marital status, education level, height and weight, income, household size, disability compensation status, lawsuit status, employment status) for descriptive purposes. We will also ask participants about their chronic pain history, chronic pain treatment and surgery history, whether they have been out of work due to chronic pain, smoking and alcohol use, treatment preferences, pain medication beliefs, and CT, MM, and AS treatment history and practice.

The baseline data and demographic questions will take approximately 20-30 minutes to complete, and may be completed following enrollment during the same phone call as the informed consent session or during a later call if more convenient for the participant. Research staff will record baseline and demographic data on an electronic case report form in REDCap.

The collection of baseline data and demographic information may take place up to seven weeks prior to the start of the treatment groups for that particular cohort. Staff may collect information on a participant's age, sex, gender, race, and ethnicity immediately after informed consent and prior to the start of the Pre-Treatment Phase (i.e., before the window for baseline and demographic data collection opens).

We will re-collect baseline and demographic information if 3 months or more have passed since collection of this information and randomization. In other words, if a participant has already provided baseline and demographic information, but continues to defer to later cohorts without yet being randomized, the last instance of baseline and demographic information on file for them must have been collected within 3 months of randomization, regardless of the number of times the baseline and demographic information was already collected.

D6e. Personal Contact Information

Research staff will collect the following information from participants: (1) contact information; (2) preferred telephone number to reach an individual if they have more than one line; (3) permission to leave message on mobile/landline phones; (4) permission to send a text message and, if yes, cell phone carrier; (5) best times/days to reach participant; (6) email address; (7) preferred communication method; (8) an emergency contact; and (9) names and contact information of people staff are allowed to contact if participant is lost to follow-up or otherwise cannot be contacted (i.e., collateral contacts). The purpose of this is to maximize the likelihood of reaching a participant to complete the study procedures. Furthermore, asking permission to leave a voicemail at a specified contact number ensures a greater level of privacy for the participant.

The information may be collected following enrollment either during the same phone call as the informed consent session or during a later call if more convenient for the participant.

D6f. Technology Training Session

After providing informed consent but prior to randomization, a staff member will schedule a time mutually feasible with the participant to test their ability to use the HIPAA-compliant Zoom videoconferencing platform used to deliver the treatment sessions (https://zoom.us) and additionally review other study components. Zoom videoconferences allow participants to see and hear each other, and also allows screen sharing, giving therapists the opportunity to display visual information (e.g., PowerPoint slides) during the session. Staff will send the participant an invitation to join a test meeting where s/he will give a brief overview on how to operate the basic Zoom functions as a participant in the treatment sessions. Staff will also review the EMA and ActiGraph technologies with the participant during this training session. This training serves as an opportunity for staff to help address any technological issues, concerns, or questions the participant may have with their smartphone, computer, webcams, microphones, etc. and using the videoconferencing software, or with the EMA software or ActiGraph. A participant may request refresher training at a later date. Staff can also offer refresher trainings during later

cohorts if a participant does not participate in the treatment groups for the cohort which s/he completes the technology training.

The participant must verbally agree during the training session that they are comfortable with using all study-required software and with participating in group sessions using the videoconference software. We want participants to feel comfortable using all required technology before treatment starts to minimize the risk of disruptions during the treatment sessions (although staff will be on hand to help if such technological issues arise).

Written instructions on using the videoconference platform and some etiquette guidelines will also be provided to the participant.

If a participant defers to another cohort after completing the technology training session, they will need to redo the technology training (could be a refresher) at the time of the cohort for which they will receive treatment.

D6g. Assessments: General Assessment Overview

Participants will complete a Pre-Treatment extended outcome assessment with research staff following enrollment into the study. Extended outcome assessments at Pre- and Post-Treatment will be administered over the telephone by research staff blind to participant treatment assignment. The Pre-Treatment assessment may be scheduled to be done on the same day as the initial intake after the participant has provided informed consent or on a later day that works better for the participant.

During the Pre-Treatment assessment, research staff will ask participants questions on pain interference (our primary outcome), pain catastrophizing, cognitive processes, activity level, average intensity of chronic pain over the past 7 days, mood, physical function, sleep, depression, anxiety, PTSD, medication and cannabis use, pain self-efficacy, health care use, disability due to chronic pain, engagement in activities, quality of life, employment status, weight, mindfulness, pain resilience, pain beliefs, pain medication beliefs, and perceived cognitive abilities. Effective 2020, there are also questions on COVID-19's impact on mental health and well-being. Research staff will record extended outcome assessment data on an electronic case report form in REDCap.

The entire time required to answer questions during the Pre-Treatment assessment is 45-60 minutes. Participants must complete the Pre-Treatment assessment no more than 7 weeks before starting treatment and before beginning the 2-Week EMA and ActiGraph Baseline Monitoring Period described below. Participants who do not complete the Pre-Treatment assessment within this window will not be randomized and will be offered the option to defer to a later cohort. If a participant completes the Pre-Treatment assessment but defers to a future cohort before getting randomized, s/he will need to redo the Pre-Treatment assessment at the time of the future cohort as we require this data within 7 weeks of treatment.

The assessment period described above will be completed prior to initiating treatment, post-treatment (after session #8), and 3 and 6 months following the end of treatment for a total of four times. These assessment periods that occur following the start of treatment will also include questions about amount of time spent practicing skills learned in treatment, treatment satisfaction and treatment modality, and overall improvement since the participant began the treatment program. The assessments done at 3 and 6 months following the end of treatment

may be completed online by the participant via REDCap instead of verbally over the telephone with research staff. Regardless of modality, the items on both the online and verbally administrated versions of the extended assessments will be the same.

The participant will also be asked additional questions at post-treatment about their experiences in the group, as well as any feedback about the treatment program. Effective 2020, there will also be a question on COVID-19's impact during treatment. These questions will be collected by an unblinded staff member and should take approximately 15-30 minutes to complete. We will audio record and code up to 100 of these interviews until we reach saturation of themes. The audio recordings will not be labeled with any identifying information. The only identifying information that will be contained within the recordings will be participants' voices and if the staff member states a participant's name during the interview.

Staff will send the participant a reminder through his/her preferred method of communication prior to the 3- and 6-month assessment periods. All scheduled telephone assessments will be completed at a time deemed mutually agreeable by both the participant and research staff. For assessments completed online, the participant will be allowed to independently complete the assessment on their own time, with limits set by researchers on how long they may spend completing the assessment (e.g., once opened, the assessment must be completed within 24 hours, 48 hours, etc.). If a participant starts an assessment within window for an assessment period but continues to provide data for that assessment after the window closes, researchers will keep the out-of-window data. This scenario could occur if the participant, for example, begins an assessment over the phone or online, has to stop, and does not complete the remainder of the assessment until after the window has closed. Although research staff have internal protocols on reminding participants a reasonable number of times to complete unfinished and partial assessments, it is ultimately on the participant to agree to finish what they started. In some cases, participants may have circumstances that prevent them from timely finishing what they started in window, despite the best efforts of research staff. Collecting and retaining the out-of-window data will NOT be considered a protocol deviation.

As mentioned above, during the consent process research staff will provide participants with a response key to help answer questions asked during the telephone assessment periods. Participants may request research staff send another response key to them if they lose the key during study participation. Research staff will send the response key along with a cover letter if the participant requests it via USPS mail or through email if the participant prefers email.

Participants will be compensated $25 for the completion of each assessment period via a check. The check will be sent via USPS mail and accompanied by a payment cover letter.

D6h. Optional Assessments

For all extended assessment periods, upon completing the main assessment, participants will be invited to participate in an optional assessment consisting of measures that were not included in the main assessment due to concerns regarding assessment length and participant burden. The optional assessment should take approximately 20-30 minutes to complete, and consists of questions regarding further responses to pain, goals, and future expectations. Optional outcome assessment data will be recorded on an electronic case report form in REDCap.

Participants are informed all optional assessments are completely voluntary, and that they may refuse to complete the optional assessments (or stop them at any time) with no effect on their payment for their completion of that particular assessment period. Participants will be informed they will not be compensated for completing the optional assessments.

D6i. Re-Assessment of Pain Interference

A participant's level of chronic pain interference for general activities will be re-assessed following consent and enrollment into the study to ensure that pain interference still meets study entrance criteria. Participants will be asked the exact same screening question they were asked initially, and a participant must answer with a pain interference score of ≥3 for general activities within the past 3 months to remain in the study. Participants who score less than 3 will be thanked for their time and withdrawn from the study.

The same pain consistency and pain frequency questions that were asked at screening will be re-assessed during the Pain Interference Re-Assessment. If inclusion criteria for pain consistency and frequency are not met at re-assessment, the participant will be withdrawn from the study.

If the participant's level of pain interference is ≥3 at re-assessment (and consistency/frequency criteria are also met), study staff will also administer an additional measure of pain interference, the Roland Morris Disability Questionnaire (RMDQ). The participant's score on the RMDQ will be used as one of the strata for randomization.

These two assessments of pain interference may be completed up to 7 weeks before the start of treatment. Participants will not be compensated for completing these assessments.

D6j. General EMA and ActiGraph Monitoring

EMA Surveys

Cue-elicited EMA will be administered via EMA software programmed to alert participants daily within two pre-set 120-minute blocks (via notifications for smart phone users and email messages for tablet, laptop, or desktop users) to complete the EMA surveys in the morning and evening. Participants will have the option to complete the survey via smart phone, tablet, laptop, and/or desktop. EMA surveys will be completed during three time periods: 2-Week Baseline, Treatment, and 4-Week Post-Treatment. The EMA software is both HIPAA-compliant and fully validated for 21 CFR Part 11; the software itself and collected EMA data will also be hosted on a secure server. Research staff will periodically download de-identified survey data from the EMA system directly onto our department's secure server for indefinite storage.

Staff will use the participant's chosen method of receiving EMA surveys to program this modality for the participant in the EMA software. That is, for participants electing to receive survey notifications through smart phone, research staff will set up the participant in the EMA management system to receive notifications with access to the survey during each morning and evening time window. For participants electing to complete surveys through a web browser, research staff will employ a similar system in which emails with a link to access the survey will be automatically emailed during each morning and evening time window. All participants will be given three pre-determined options for the morning and evening blocks for receiving surveys: for example, 5-7 AM and PM, 6-8 AM and PM, or 7-9 AM and PM. If none of the pre-determined

time blocks work for the participant, the research team may work with the participant to find suitable morning and evening blocks where the participant is better able to complete his/her surveys.

Research staff will provide the participant with verbal instructions on how to complete the EMA surveys based on their preferred survey modality during the technology training session. These instructions will also be mailed/emailed to the participant so s/he can refer to them in the future.

The 2-Week Baseline Monitoring Period will consist of an approximately 14-day period before the participant begins his/her first session of treatment. We will schedule all participants to start the Baseline Monitoring Period 14 days before the start of the first group of that cohort. This means, for example, if the first session of CT will be 4/16, the first session of MM will be 4/17, and the first session of AS will be 4/18, all participants will begin the Baseline Monitoring Period on 4/2, which is 14 days before the start of the first group (4/16). Participants will complete Baseline EMA surveys until the day before their first treatment session.

The 2-Week Baseline EMA survey asks questions on pain interference, pain catastrophizing, cognitive processes, average pain intensity during the past 12 hours, mood, pain self-efficacy, sleep/wake times, and activity level and activity monitor wear. On days before Session 1 in the evening EMA there will also be questions on treatment credibility and expectancies. Each EMA survey should take approximately 5 minutes to complete. There are a minimum of 28 EMA surveys for the participant to complete during the Baseline EMA Monitoring Period.

The Treatment Monitoring Period begins on the day the participant is scheduled for Session 1 and ends the day s/he is scheduled for Session 8. The Treatment EMA survey asks the same questions as the 2-Week Baseline EMA survey described above, with the addition of items on therapeutic alliance, group cohesion, and time spent practicing skills learned in treatment. The therapeutic alliance and group cohesion items will be added after the Session 4 and 8 evening EMAs, while the time spent practicing skills items will be asked daily during the evening EMA beginning with Session 1. Additionally, items on treatment credibility and expectancies will be asked once again after Session 1 and before Session 2. While not collected as data, there is also an additional question asked the evening before each treatment session on whether the participant has completed his/her homework activities; this question is used as a reminder to prompt participants to complete their homework activities if they have not already done so.

The total number of EMA surveys for the participant to complete during the Treatment Monitoring Period will vary depending on the schedule of the sessions. While we aim to have sessions twice a week for four consecutive weeks, this may not be the case if there is a holiday which the UW is closed or a session needs to be rescheduled for a variety of reasons. Participants will continue to complete EMAs daily during the entire Treatment Monitoring Period, regardless of the scheduling of sessions.

Finally, the 4-Week Post-Treatment Monitoring Period begins the day after Session 8 and extends for four weeks. The 4-Week Post-Treatment EMA survey asks the same questions as the Baseline EMA survey described above minus the items on treatment credibility and expectancies but with the addition of time spent practicing skills items. There will be a total of 56 EMA surveys for the participant to complete for the 4-Week Post-Treatment Monitoring Period.

Research staff will monitor the EMA data daily for possible missing responses and employ an internal protocol for contacting the participant regarding missed surveys. This protocol will be strict enough such that participants who are not completing surveys are followed up appropriately, but also allow enough flexibility so that the number of contact attempts is reasonable and will depend on where the participant is in study participation and their unique circumstances. For example, a participant who has withdrawn from treatment due to issues of time commitment but remains intent-to-treat may warrant less frequent contacts about missed surveys compared to someone who remains in treatment and is fully engaged.

If a participant defers to a future cohort after starting the 2-Week Baseline Monitoring Period but before getting randomized, s/he will need to redo the 2-Week Baseline Monitoring Period at the time of the future cohort as we require a minimum 14 days of EMA collection prior to treatment.

Participants will be compensated $1 for the completion of each EMA survey, plus a $6 "bonus" for each week they complete ≥12 surveys. At the end of each EMA Monitoring Period, the number of EMA surveys completed will be tallied and total payment calculated for the entire period. A single check for the total payment for EMA surveys completed for that period will be sent via USPS mail and accompanied by a payment cover letter.

ActiGraphs

Activity levels and sleep will also be measured during these three time periods using the ActiGraph wGT3X-BT, which uses triaxial accelerometry that has been shown to be a valid measure of daily physical activity in people with chronic pain,[94] and provides a more valid and reliable assessment of activity level than self-report methods.[95] The ActiGraph will be worn all day (except when the participant is showering, swimming, etc.), including during sleep. The participant would wear the ActiGraph like a wrist watch on his/her non-dominant arm. There is no risk of electric shock with this device.

Research staff will provide the participant with verbal instructions on the use and care of the ActiGraph during the technology training session. These instructions will also be mailed/emailed to the participant so s/he can refer to them in the future.

ActiGraphs will be mailed out to all participants in a cohort about one week prior to the beginning of the 2-Week Baseline Monitoring Period to minimize the risk of participants losing the ActiGraph. ActiGraphs will only be mailed if the participant has completed all of the required baseline procedures that are scheduled to occur before the beginning of Baseline Monitoring (including the Baseline Assessment, Pre-Treatment Extended Assessment, Pain Interference Re-Assessment, and Technology Training). Participants will also be instructed to fully charge the ActiGraph using the provided charging cables before first use, and as needed throughout (i.e., when the monitor light begins to flash red – typically after approximately 1-week of consistent wear-time).

The participant will be instructed to send back the ActiGraph in a provided self-addressed stamped envelope at the end of the 4-Week Post-Treatment Monitoring Period. Research staff will download all data collected by the ActiGraph and link it to the participant's other data via his/her participant identification number. Data may be downloaded directly from the ActiGraph only with the assistance of ActiLife software that is unavailable to the general population. That is, participants will NOT have the ability to download the data from the device itself (e.g., onto their personal computer). The data will be stored on a secure server in de-identified form indefinitely.

Research staff will monitor ActiGraph wear compliance through questions on the EMA survey. Specifically, there is a question on the evening EMA asking the participant if s/he wore the device at all times during the past 24 hours. If a participant answers “No”, a follow-up question will ask approximately how long they were not wearing the device. A staff member will employ an internal protocol for contacting the participant regarding ActiGraph non-wear. This protocol will be strict enough such that participants who are not wearing the device are followed up appropriately, but also allow enough flexibility so that the number of contact attempts is reasonable and will depend on where the participant is in study participation and their unique circumstances. For example, a participant who has withdrawn from treatment but remains intent-to-treat AND who has reported difficulties with wearing the ActiGraph may warrant less frequent contacts about non-wear compared to someone who remains in treatment and is fully engaged.

If a participant defers to a future cohort after starting the 2-Week Baseline Monitoring Period but before getting randomized, s/he will need to redo the 2-Week Baseline Monitoring Period at the time of the future cohort (i.e., s/he will need to wear the ActiGraph again).

Participants will be compensated $70 for the return of the ActiGraph after the 4-Week Post-Treatment Monitoring Period. The check will be sent via USPS mail and accompanied by a payment cover letter.

To encourage wear compliance and the timely return of activity monitors, we will also offer participants the option to receive a summary of their ActiGraph data at study completion (after they have finished the 6-Month Extended Assessment). If the participant desires, we will send them either via USPS postal mail or email a document that may include data on one or more of the following: activity counts, energy expenditure, MET rates, steps taken, physical activity intensity, sleep latency, total sleep time, wake after sleep onset, and/or sleep efficiency. This information will be sent with a cover letter.

Participants who do not return their ActiGraphs within a reasonable amount of time will be contacted by research staff via phone, email, text, and/or letter to encourage the participant to send the device back as soon as possible. We will only have a limited number of devices on hand and need the devices back promptly to ensure we can 1) collect the stored data and 2) have enough devices ready to deploy for the next return point/next cohort of participants.

D6k. Randomization

We will begin randomizing participants no sooner than six days after the start of the 2-Week Baseline Monitoring Period and continue to randomize until the day before the first treatment group starts. All participants in the current cohort will be reviewed to see if they completed all required baseline procedures and are thus eligible for randomization. The required baseline procedures are as follows:

1. Provided Baseline data and Demographics;
2. Completed Pre-Treatment Assessment;
3. Participated in technology training session and verbally agreed they are comfortable with all study software and with participating in group sessions using the videoconferencing software;
4. Completed re-assessments of pain interference and frequency/consistency;

5. Completed at least 7/14 EMA surveys during Week 1 of the Baseline Monitoring Period.

All participants need to complete the above required baseline procedures before they will be randomized; however, exceptions to meeting all randomization criteria may be given by researchers on a case-by-case basis should there be any extenuating circumstances that prevent the participant from meeting all randomization criteria. For example, a participant could have trouble accessing or completing EMAs not due to lack of participant effort. Participants who do not meet the EMA completion criterion above may be offered the opportunity to be contacted in the future should the criterion be revised. At that point, they would be re-screened for eligibility and will re-complete any Baseline procedures that are needed. If the Baseline procedures are completed the subsequent time around, then the participant will be eligible for randomization.

Participants who are not randomized will be asked to mail back any ActiGraphs still in their possession. Randomization will use a covariate-adaptive randomization scheme. We will use a procedure proposed by Pocock and Simon (see Chapter 9 of Randomization in clinical trials: Theory and practice, 2nd edition, 2016, by W.F. Rosenbeger and J.M. Lachin, John Wiley and Sons), with the objective of balancing the covariate in the marginal distributions. The covariates for the covariate-adaptive randomization will be sex, baseline pain interference score (mild/moderate or severe), and low back pain (LBP) type (primary or secondary pain).

The implementation of the procedure will be accomplished by using a statistical program, such as R. The study statistician will write the program and will be responsible for running the randomization for each cohort; the statistician may also train another staff member to be a backup randomizer should s/he be unavailable to randomize participants for a cohort (e.g., away on vacation and cannot access the program). When a new cohort is ready to be randomized, the staff responsible for enrollment of the participants will provide the statistician with a list of participants (identified by dummy ID number and not their actual subject ID number) with their respective values of the covariates (sex, pain interference at baseline, and LBP pain type). The statistician will randomize according to the Pocock and Simon procedure, and return the list to the staff member responsible for creating the treatment groups according to the assignments. The staff member will then match the dummy ID numbers with the list containing the actual subject ID numbers. For example, the staff member responsible for enrollment may send a list of dummy IDs A, B, and C to the statistician. There will be a separate list (which the statistician does not have access to) linking subject ID to the dummy ID (e.g., A = 800009, B = 812349, C = 822229). The statistician will randomize A, B, and C to treatment and send back these assignments to the staff member; the staff member will then input the subject ID into the randomization list by matching the dummy ID to the subject ID. There is no potential for staff bias to interfere with creating these lists or randomizing participants. ***This is because the staff member conducting randomization will never have access to any person level information (other than sex, pain interference category, and LBP type), nor will the staff member have any direct communication with study participants at any point.*** Further, even if the staff member was familiar with person level details, this would not impact the structure of the randomization list, given that the order in which participants from each block are randomized is determined automatically by the program created by the statistician. To further safeguard against potential bias, individuals will be randomized in the order that they become eligible for randomization (based on the completion of the pre-randomization procedures). After a participant has been randomized, the research staff member in charge of data entry will update the randomization form in REDCap to reflect the participant's treatment allocation. Only staff members who do not have access to study data during participant enrollment will know

which treatment intervention corresponds with which group. Research staff will complete an electronic randomization case report form for each randomized participant that will be included with study data. The master list of participants will also be updated with the participant's assignment.

An unblinded staff member will call the participant to convey assignment and the schedule of treatment sessions. Brief (1 page) reading material specific to the treatment group will also be made available to the participant in preparation for Session 1; the reading material is informative only and not home practice. The group schedule and reading material will be provided to the participant electronically, unless the participant requests otherwise. The unblinded staff member may also provide the participant part or all of their participant treatment handbook prior to the first session (excluding instances in which the treatment mandates that a given portion of the treatment materials not be provided before a particular treatment session).

Research staff will re-screen participants on approved mutable eligibility criteria (e.g., pain intensity, frequency, etc.) if three months or more has elapsed between the consent process and randomization.

D6l. Treatment Scheduling

Cohorts of study treatment groups will be offered 3-5 times per year.

Trained clinicians will commit to offering at least three groups per year: one of each treatment type. This will reduce the potential for therapist bias on the outcomes.

An unblinded staff member will maintain lists of group assignments and coordinate the scheduling of sessions. Staff will provide clinicians with a list of participants who were assigned to each class. Treatment reminders will be provided for each session using the participant's preferred method of communication. If a participant misses a session, the therapist or another staff member may contact the participant about the missed session. If the therapist or other staff member is not able to get a hold of the participant, additional follow-up may be conducted by research staff.

D6m. Treatment

Participants will attend eight 90-minute group treatment sessions scheduled on average twice per week for four weeks. In all three treatment conditions, group sessions will be conducted via the online, HIPAA-compliant Zoom videoconferencing platform (https://zoom.us/) with support from UW IT Services. Zoom videoconferences allow participants to see and hear each other, and also allows screen sharing, giving clinicians the opportunity to display visual information (e.g., PowerPoint slides) during the session. In the event that a participant cannot access the videoconference during a specific session, we will provide workbooks to follow along with and to facilitate skills practice outside of sessions.

Participants may participate in Zoom sessions through a smart phone, tablet, laptop, or desktop computer. All participants will be provided instructions and training prior to their first scheduled session on how to log in, join the session, set up their video/audio components, and how to navigate the various menus/buttons within Zoom. Finally, participants are required to participate in sessions in a quiet, private location free from distractions to maximize treatment

engagement and to protect the privacy and confidentiality of the sessions (e.g., their home or private office).

The group sessions will be conducted by PhD- or Masters-level clinicians with at least two years of clinical experience and who have undergone training that prepares clinicians to conduct each of the three treatment interventions in a group setting. The study clinicians will be trained and supervised by the investigators who have a great deal of experience in providing the study treatments. The clinicians will be provided with a detailed treatment manual and protocol outline, and Drs. Ehde (CT intervention), Day (MM intervention), or Jensen (AS intervention) will provide regularly scheduled (weekly for the first two cohorts facilitated by any new study clinician; this may decrease to twice monthly once the study clinician has experience with the interventions and has demonstrated at least 90% treatment fidelity for the interventions provided) supervision for the study clinicians.

We will have a goal of having each group led by one or two clinicians allowing for groups to continue as scheduled in the event one of the clinicians is unable to attend a particular group.

Additional participants will be scheduled for the groups until they reach the maximum size. Clinicians will be expected to follow closely the treatment manuals to ensure all scheduled material is covered, and to ensure the consistency and replicability of treatment.

In all conditions, home practice activities will be assigned to build skill and competence in the coping techniques taught in the treatment sessions. While the exercises in MM are experiential in nature, the CT and AS conditions include didactic, written exercises. To assist with facilitation of learning between sessions, and to have record of engagement in home practice, all participants will be asked to keep an electronic record of their between-session activities. Participants in the CT and AS conditions will be asked to record the didactic components on Google Drive forms that are electronic versions of the forms provided in the participant handbooks; participants in the MM condition will be asked to write about the nature of their experiential learning during the MM practice on Google Drive forms that will also be electronic versions of the forms provided in the MM participant handbooks. Participants will be asked to complete electronic versions of these forms by the evening before each treatment session (with the exception of the first session); participants may also directly email their homework to clinicians. Participants will be instructed not to put their names or any identifying information on the forms. Clinicians will review these forms before the sessions in order to clarify any problem(s) the participants may have had between sessions. The completed forms will be downloaded and engagement in home practice data will be extracted and stored. Copies of these home practice forms will be stored on the department's secure server.

Participants who have not completed the form by the morning of the session may, time permitting, be called to remind him/her to complete the form before the session starts.

We realize that adherence to interventions assigned outside of treatment sessions may influence study outcomes so will utilize EMA data collected about homework compliance. In addition, all participants in all interventions will be given a treatment workbook with materials to refer to and discuss during the group sessions as well as additional materials to read between sessions.

Cognitive Therapy (CT) condition

The cognitive-restructuring technique[7,96] will be used to help patients recognize the relationships between thoughts, feelings, behaviors and pain. This technique will help patients:

(1) identify negative or unrealistic automatic thoughts; (2) evaluate automatic thoughts for accuracy, identify sources of distorted thoughts, recognize the connection between automatic thoughts and emotional/physical shifts; (3) challenge negative, distorted automatic thoughts via "weighing the evidence"; (4) develop new realistic alternative cognitive appraisals; and (5) practice applying new rational appraisals and beliefs.

Participants in the CT condition will be asked to complete a Record of Automatic Thoughts Concerning Pain each day between sessions throughout the duration of treatment. It includes identification of the situation, automatic thoughts, emotional responses, and physical responses, as well as questions designed to challenge automatic thoughts and generate more reassuring thoughts. Other less formalized homework assignments may also be assigned, including practicing other cognitive skills learned in treatment (e.g., thought-shifting techniques, coping statements).

Mindfulness Meditation (MM) condition

Participants will receive training in mindfulness meditation, specifically Vipassana, which is the form of meditation typically implemented in mindfulness research.[8] With this technique, the emphasis is placed upon developing focused attention on an object of awareness, e.g., the breath. This focus is then expanded to include a more open, non-judgmental monitoring of any sensory, emotional, or cognitive events. A standard script will be implemented by the clinician, and participants will be seated in a comfortable yet alert position.

In addition, participants will be given pre-recorded recordings of the meditation technique taught in the sessions and encouraged to practice MM daily (first using the recordings, and then later, on their own without recordings). Participants will be asked to listen to the recordings as often as they find helpful, but particularly at the time of the day they feel more alert, avoiding using them before going to sleep. Both a 20-minute as well as a 40-minute version will be provided to participants; although clinicians should encourage participants to practice the full 40-minutes, the 20-minute version is provided as this shorter version may especially be helpful early on in treatment, when participants are introducing a "new habit" of meditation in to their daily routine. They will also be encouraged to experience mindfulness meditation multiple times during each day (at least 3 times) by engaging in a short, 3-minute breathing space meditation focusing on the movements of the breath. Participants in the MM condition will be asked to fill out a practice log where they will describe what the mindfulness meditation practice experience was like for them.

Activation Skills (AS) condition

Participants will be educated about the role of inactivity and behavioral avoidance in chronic pain and functioning. They will learn how to be aware of the activities they avoid because of pain, and how to set effective goals so that, step by step, they can start being more active and resume some activities they enjoyed in the past but are currently avoiding. Explanation and practice of a set of specific skills – including appropriate pacing skills – to facilitate an increase in appropriate activity level will be provided.

Participants in the AS condition will be asked to complete an activity log where they self-record their daily activities. Participants will also be asked to complete daily Goals Review and Success Logs, where they will record their short-, medium-, and long-term activity goals, taking into account different types of goals and the characteristics of effective goals (specific, measureable, achievable, relevant, and time-bound [SMART]).

Please note that the overall content of the treatment interventions as described above will not change during the course of the study. However, minor revisions of the actual therapist manual and participant workbook, such as minor changes to formatting and specific language (i.e., revisions that do NOT result in a change in the risk/benefit ratio or to the substance of the material covered), are anticipated throughout the study due to the iterative process of developing a psychotherapeutic treatment intervention.

Attendance Records

Group leaders (clinicians) will be given an electronic roster of the anticipated participants in their group. The roster will only include a participant's name, participant ID, and basic contact information should the clinician need to get a hold of the participant. The clinician will record the participant's absence or presence for each session on an electronic attendance form in REDCap. Only unblinded staff members will have access to these records, and the records will be password-protected and stored on a limited access folder on our department's secure server.

Treatment completion will be defined as attending at least 4 of the 8 total group sessions.

Data Collected during Treatment Sessions

Participants will complete via Google Drive a form regarding their completion of tasks or "homework" assigned by the clinician from the previous session. This form does not contain identifying information and the participant will be instructed not to put their name on it. Clinicians will review these forms before the sessions in order to clarify any problem(s) the participants may have had between sessions. All homework forms will be downloaded and stored on our secure network drive.

Study clinicians will also complete for each participant in that particular session a measure of perceived engagement within group after the session is over.

In this way, we address an important scientific question (i.e., whether engagement in homework and experience within sessions is associated with outcomes), but none of the clinicians are directly engaged in outcome data collection, and there is no additional burden to the participants.

Audio Recordings

All group treatment sessions will be audio recorded using Zoom's built-in recording function to ensure compliance to treatment procedures. These recordings may also be used for training purposes. A portion of treatment sessions will be randomly selected and reviewed/coded by study researchers to ascertain fidelity to protocol. Study clinicians will receive feedback during regularly scheduled supervision sessions with either Drs. Ehde, Day, or Jensen (depending on treatment condition) and corrective feedback will be provided as needed if they diverge from protocol.

The study clinicians will notify participants before the start of the session that s/he will be recording the session, and all participants in the group must have provided consent to audio record during the informed consent process. Participants who withdraw their consent to record after the groups start but who still want to participate in the study may still complete all remaining study procedures with the exception of treatment sessions.

Audio recordings will only be reviewed by study personnel and used for assessing consistency between study clinicians. The audio recordings will not be labeled with any identifying information. The only identifying information that will be contained within the

recordings will be participants' voices and if the study clinician or if group members state participants' names during the discussion.

Treatment Intervention Discontinuation

A participant will be withdrawn from the treatment intervention if s/he (1) engages in behavior that is disruptive to the group, and/or (2) engages in behavior that interferes with the appropriate administration of the group treatment.

However, participants who are withdrawn from the study treatment intervention will be invited to complete study assessments at post-treatment, 3-month, and 6-month follow-up as well as any remaining EMA surveys and continue to wear the ActiGraph to allow for complete data for the planned intent-to-treat analyses (see below). Participants will receive payment for the time it takes to provide outcome data at each assessment point.

An electronic treatment withdrawal/termination case report form will be completed for participants who withdraw or are terminated from treatment.

Intent-to-Treat (ITT)

For all participants who are randomized to receive one of the three study treatments but are unable to participate in that cohort's treatment sessions, the participant will always be asked to complete study assessments for that cohort and included in study analysis unless they withdraw their participation from the study. This means that, post-randomization, if a participant is unable to attend the treatment s/he was assigned to OR decides to withdraw from treatment, s/he will be offered the opportunity to continue with EMAs, wear the activity monitor, and complete extended assessments for that cohort in which randomization had occurred. The participant will not be allowed to defer to another cohort to participate in treatment. Once a participant is randomized, s/he cannot be deferred to a later treatment cohort, even if they do not participate in a single session of the cohort they are randomized in. If a participant needs to defer to another cohort, this is only allowed **before** they have been randomized.

D6n. Study Design Enhancements: Treatment Fidelity, Missed Sessions and EMA Assessments, Participant Engagement, and Study Retention Strategies

We will take a number of steps to ensure uniform treatment protocol delivery. First, all treatments will be provided by a Masters-level clinician, postdoctoral senior fellow, or licensed psychologist (the study "clinician") who has at least two years of clinical experience in delivering psychosocial treatments or by one of the study investigators. The clinician will be trained and supervised by the investigators who have a great deal of experience in providing the study treatments. If one of the study clinicians is unable to deliver a session as planned, and no other study clinicians are available to fill in, a clinician who has experience in delivering the treatment content may be asked to fill in during emergency situations. This emergency clinician would have documentation of training from any of the study investigators or consultants demonstrating training in the content of the session being covered. Second, the clinician will be provided with a detailed treatment manual and protocol outline. Third, Drs. Ehde (CT intervention), Day (MM intervention), or Jensen (AS intervention) will provide regularly scheduled supervision to the study clinicians. Weekly supervision will occur for the first two cohorts of every study clinician new to the program; these are anticipated to become less frequent as the clinicians gain more experience and the need for frequent supervision sessions decreases. However, all clinicians at all times will have easy access to the clinical supervisors (either in person, via telephone, via email, or via Skype) at any time between the supervisory sessions as needed and as issues

arise. Fourth, adherence and fidelity will be monitored using session audio recordings. Masters-level or above clinicians supervised by the investigators will review a random selection of 25% of the recordings (2-3 randomly selected sessions per group, to be coded by the start of treatment for the following cohort) to ensure procedures are followed. Protocol quality and adherence criteria will be developed for each session with satisfactory adherence defined as ≥90% of the maximum possible score. Corrective feedback will be provided to the clinician during regularly scheduled supervision sessions; didactics and role plays to correct "drift" will be implemented if needed.

We will monitor session attendance and session dates to track percentage of attendance and to account for absenteeism and reasons for any missed sessions. Reasons for attrition will be assessed for participants who withdraw. Given clinician-rated participant engagement during sessions was associated with dropout in our preliminary research,[38] we will assess this at each session for each participant. Enactment of treatment-specific changes will be assessed by homework practice, assessed via EMA. Comparisons between the treatment conditions in dropout rates will be made, and variables shown to differentiate the groups will be included as covariates.

To minimize possible missed EMA data, we will provide financial incentives for completing the EMA surveys (i.e., $1.00 per assessment, plus a $6.00 "bonus" for each week they complete ≥12 assessments). In addition, a staff member will monitor the EMA data daily for possible missing responses and employ an internal protocol for contacting the participant regarding missed surveys. This protocol will be strict enough such that participants who are not completing surveys are followed up appropriately, but also allow enough flexibility so that the number of contact attempts is reasonable and will depend on where the participant is in study participation and their unique circumstances. For example, a participant who has withdrawn from treatment due to issues of time commitment but remains intent-to-treat may warrant less frequent contacts about missed surveys compared to someone who remains in treatment and is fully engaged.

To minimize possible missed ActiGraph data, research staff will monitor ActiGraph wear compliance through questions on the EMA survey. Specifically, there is a question on the evening EMA asking the participant if s/he wore the device at all times during the past 24 hours. If a participant answers "No", a follow-up question will ask approximately how long they took the device off. A staff member will employ an internal protocol for contacting the participant regarding ActiGraph non-wear. This protocol will be strict enough such that participants who are not wearing the device are followed up appropriately, but also allow enough flexibility so that the number of contact attempts is reasonable and will depend on where the participant is in study participation and their unique circumstances. For example, a participant who has withdrawn from treatment but remains intent-to-treat AND who has reported difficulties with wearing the ActiGraph may warrant less frequent contacts about non-wear compared to someone who remains in treatment and is fully engaged. If the participant says s/he cannot wear the ActiGraph due to skin irritation, researchers will provide the participant with a more comfortable way of wearing the ActiGraph on the wrist (e.g., using a softer material on the wrist strip).

To encourage wear compliance and the timely return of ActiGraphs, we will also offer participants the option to receive a summary of their ActiGraph data at study completion (after they have finished the 6-Month Extended Assessment). If the participant desires, we will send them either via USPS postal mail or email a document that may include data on one or more of the following: activity counts, energy expenditure, MET rates, steps taken, physical activity intensity, sleep latency, total sleep time, wake after sleep onset, and/or sleep efficiency.

Participants who do not return their ActiGraphs within a reasonable amount of time will be contacted by research staff via phone, email, text, and/or letter to encourage the participant to send the device back as soon as possible.

We will implement a number of strategies to maximize participant retention. For example, sessions will be offered at different times, on a recurrent basis, giving participants scheduling flexibility. All research staff that interact with participants will be taught listening skills and encouraged to be warm in all interactions to enhance rapport. The on-site co-PI, Dr. Jensen, will receive weekly reports from staff so the investigators can discuss recruitment and retention during the scheduled research meetings and quickly implement changes if needed.

Finally, participants will receive up to $100 remuneration for completing all telephone-administered extended assessments, $1.00 per each EMA survey, plus a $6.00 "bonus" for each week they complete ≥12 EMA surveys, and up to $70 for mailing back their ActiGraph(s). We have successfully used these and other strategies in our past trials, with a retention rate of 85% to 97%.[41,56,66,97]

Replacement Check Protocol

Research staff will send participants with a check that is outstanding 180 days after issuance of a letter/email that:

- Notifies the participant that the check remains uncashed;
- Requests the participant indicate whether they would like a new check(s) or decline payment; and
- Instructs the participant to sign the reissuance form and send it back to research staff in the included self-addressed envelope.

Research staff will then issue a new check to participants who request new check(s). Research staff will contact participants who have not returned the signed form within 2-3 weeks of mailing. Research staff will send out the same letter/email again if requested by participants.

Research staff will send the same letter/email described above to participants who notify staff that they did not receive the check/lost it, and request a replacement check.

D6o. Study Completion

Participants we are unable to get a hold of during the course of the study we may mail an "unable to contact letter" requesting they contact study staff as soon as possible to discuss their participation. We will also attempt to reach these participants via phone, email, text, and/or through their collateral contacts.

Research staff will complete an electronic study completion form when either (1) a participant completes the 6-month assessment period, or (2) withdraws or is withdrawn from the study. Participants who complete the 6-month assessment period will be sent a cover letter along with their final remuneration with language indicating completion of the study. Participants who fail to complete the 6-month assessment period will be sent a letter/emailed informing the participant that his/her participation in the study has ended.

Table 2. Participant Involvement

Procedure	Number of Assessments	How Often / When	Time Required for Participants	Compensation
Pain Interference Re-Assessment	One telephone assessment	Once, following informed consent process; before 2-Week Baseline Monitoring Period	About 1 minute	$0
Randomization Stratification	One telephone assessment	Once, following informed consent process; before 2-Week Baseline Monitoring Period	About 5 minutes	$0
Baseline Data and Demographics Collection	One telephone assessment	Once, following informed consent; before treatment begins	About 20-30 minutes	$0
Pre-Treatment Extended Assessment	One telephone assessment	Once, following informed consent process; before 2-Week Baseline Monitoring Period	About 45-60 minutes	$25
Technology Training	One videoconference training session	Once, following informed consent process; before 2-Week Baseline Monitoring Period	About 30-45 minutes	$0
Baseline Monitoring Period*	At least twenty-eight (28) EMA assessments	Twice daily EMA assessments for approximately 2 weeks prior to first treatment session	About 5 minutes per assessment	$1 per completed EMA assessment; $6 bonus for every week with ≥12 completed
Treatment	Eight (8) videoconference group treatment sessions	Average of twice per week for approximately 4 weeks	90 minutes per session	$0
Treatment Monitoring Period*	Twice daily EMA assessments for duration of treatment	Twice daily EMA assessments, commencing on day of first treatment session, ending on day of last session	About 5 minutes per assessment	$1 per completed EMA assessment; $6 bonus for every week with ≥12 completed

Post-Treatment Extended Assessment	One telephone assessment	Once following end of treatment	About 45-60 minutes	$25
Post-Treatment Qualitative Assessment	One telephone assessment	Once following end of treatment	About 15-30 minutes	$0
Post-Treatment Monitoring Period*	Fifty-six (56) EMA assessments	Twice daily EMA assessments for 4 weeks following end of treatment	About 5 minutes per assessment	$1 per completed EMA assessment; $6 bonus for every week with ≥12 completed
Return Activity Monitor	N/A	Once, following end of Post-Treatment Monitoring Period	N/A	$70
3-Month Extended Assessment	One online or telephone assessment	Once, approximately three months following end of treatment	About 45-60 minutes	$25
6-Month Extended Assessment	One online or telephone assessment	Once, approximately six months following end of treatment	About 45-60 minutes	$25

* Participants will wear ActiGraphs for the duration of monitoring periods

D6p. Study Data

We list the demographic and descriptive information we propose to collect from the study participants in the next paragraph. The outcome variables, covariates (variables to control for in planned analyses if needed), and mechanism (mediator and moderator) variables for this study are listed in Table 3. Specific measures by time point are provided in Table 4.

Descriptive/Demographic Variables

All participants will be asked to provide demographic data (age, sex, gender orientation, ethnicity, race, marital status, education, alcohol/drug use, smoking behavior, height and weight, income, household size, disability compensation status, lawsuit status, and employment status). We will also ask about their history of MM, CT, and AS treatment and practice, as well as general chronic pain history (pain duration, pain frequency, pain intensity, other pain sources/types, surgery history, and pain interference with employment). We will also ask questions regarding co-morbid conditions (spinal stenosis and sciatica), pain medication use, and treatment preferences.

Outcome variables, covariates, and mechanism variables

Outcome variables, covariates, and mechanism variables will be assessed through a combination of extended assessments and EMA monitoring. In some cases, slightly abbreviated versions of a measure will be administered during EMA assessments in order to minimize participant burden and encourage compliance (e.g., positive and negative affect, two items are asked in EMA and ten items are asked in extended assessments). The number of items for each measure in the EMAs was selected on the basis of content validity, factor loadings established during initial measure development and validation studies, brevity, and pilot data. Building on this, the minimum number of items was then selected that achieved at least good internal consistency reliability ($\alpha \geq .80$) for the mechanism variables and excellent reliability ($\alpha \geq .90$) for the primary outcome variable of pain interference in our pilot data. All outcome measures will be administered by research staff members blind to group allocation.

Qualitative Outcomes

A one-time qualitative interview assessing participant experiences in group, as well as any feedback about the treatment program will be completed following the completion of treatment by an unblinded staff member. Effective 2020, there will also be a question on COVID-19's impact during treatment. Qualitative interviews will not be conducted for participants who do not attend any treatment sessions.

Table 3. Primary, Secondary, Co-Variate, and Mechanism Variables

Variable Type	Domain	Measure (# items EMA, Extended)
Primary Outcome	Pain Interference	PROMIS Pain Interference (5, 5)
Primary Mechanisms and Moderators	Cognitive Content	Pain Catastrophizing – Items from Pain Appraisal Scale (3, 5), Coping Strategy Questionnaire (CSQ) (2 items ext. only)
	Cognitive Process	Pain-Related Cognitive Process Questionnaire (PCPQ) Non-Judgment Scale (2, 6)
	Activity Level	Actigraphy, Godin Leisure-Time Exercise Questionnaire (3, 3), Hours spent sitting without exercising (EMA only)
Secondary Outcomes	Average Pain Intensity	Numerical Rating Scale (NRS), 0-10 (1, 1)
	Mood	Positive and Negative Affect Schedule (PANAS) (2, 10)
	Physical Function	PROMIS-29 Physical Function (4 items ext. only)
	Sleep Quality	Actigraphy, PROMIS-29 Sleep Disturbance (4 items ext. only)
	Depression	PROMIS-29 Depression (4 items ext. only)
	Anxiety	PROMIS-29 Anxiety (4 items ext. only)
	Medication Use	Medication Use Questionnaire (extended only)
	Cannabis Use	Investigator-developed items on cannabis use (3 items ext. only)
	Medication Use Attitudes	Survey of Pain Attitudes (SOPA) Medication Beliefs Sub-Scale (6 items ext. only), Pain Medication Questionnaire (PMQ) (26 items Baseline only)
	Post-Traumatic Stress Disorder	PTSD Checklist – Civilian Version (PCL-C) (0, 17)
Secondary Mechanisms	Pain Self-Efficacy	UW Pain-Related Self-Efficacy Scale (3, 6)
	Patient Engagement	Clinician reported patient engagement (5 items rated by clinician)
	Therapeutic Alliance	Working Alliance Inventory (WAI) (12 items EMA only)
	Group Cohesion	Group Climate Questionnaire (GCQ-S) Engagement Scale (5 items EMA only)
	Skills Engagement	Duration and number of times practicing skills (EMA), number of days and duration of time practicing skills (Extended)
Tertiary Outcomes	Health Care Use	# visits to health care professional in last month (1 item ext. only)
	Pleasurable Activity	Pleasant Events Schedule SF (10 items ext. only)
	Behavior Activation	Behavioral Activation for Depression Scale (BADS) (9 items ext. only)
	Quality of Life	Global quality of life (1 item ext. only)
	Employment Status	Employment question (1 item Baseline & ext. only)
	Weight Change	Weight question (1 item Baseline & ext. only)
	Patient Global Impressions of Change	Patient Global Impressions of Change (PGIC) (6 items ext. post-treatment and follow-up assessments only)
	Patient Global Assessment of Treatment Satisfaction	Patient Global Assessment of Treatment Satisfaction (PGATS) (1 item ext. post-treatment and follow-up assessments only)
Tertiary Mechanisms	Mindfulness	Mindful Attention Awareness Scale (MAAS) (15 items ext. only)
	Resilience	Pain Resilience Scale (14 items ext. only)
	Other Cognitive Processes	All other PCPQ items (47 additional items ext. only, 53 total items)
	Pain Beliefs	Survey of Pain Attitudes (SOPA) Harm, Control, and Disability Scales (18 items ext. only)
Exploratory Moderators	Cognitive Abilities	PROMIS Cognitive Function Abilities (6 items ext. only)
	Treatment Credibility	Treatment Credibility & Expectancies items (5 items EMA only)
	COVID-19	Investigator-developed items on COVID-19's effects (6 items ext. & 1 item Qualitative Interview)
Covariate	Primary Problem (LBP primary or secondary)	Baseline Self-Report
Optional Assessments	Responses to Pain	Positive & Negative Response to Pain Scales (85 items)
	Future Self	Future Self Questionnaire (FSQ) (16 items)
	Values-Consistent Goals	Valued Living Scale (VLS) (8 items)
Qualitative Outcomes	Experiences in group & program feedback	15-30" of investigator-developed qualitative items

Table 4. Study Assessment Schedule

Measures	EMA	Baseline	Pre-Treatment	During Treatment	Post-Treatment	3-Month	6-Month
Demographic Information		X					
Pain and Treatment History		X					
Start Back Tool		X					
Pain Medication Questionnaire (PMQ)		X					
Roland Morris Disability Questionnaire SF (RMDQ)		X					
PROMIS Pain Interference	X		X		X	X	X
Pain Appraisal Scale (PAS)	X		X		X	X	X
2-item Catastrophizing Scale from the Coping Strategy Questionnaire (CSQ)			X		X	X	X
Pain-Related Cognitive Process Questionnaire (PCPQ) Non-Judgment Scale	X		X		X	X	X
Godin Leisure-Time Exercise Questionnaire	X		X		X	X	X
Hours Spent Sitting w/o Exercising	X						
Pain Intensity NRS	X	X	X		X	X	X
Positive and Negative Affect Schedule (PANAS)	X		X		X	X	X
PROMIS-29 Sleep Disturbance			X		X	X	X
PROMIS-29 Physical Function			X		X	X	X
PROMIS-29 Depression			X		X	X	X
PROMIS-29 Anxiety			X		X	X	X
PTSD Checklist (PCL-C)			X		X	X	X
Medication & Cannabis Use			X		X	X	X
UW Pain-Related Self-Efficacy Scale	X		X		X	X	X
Participant Engagement				X[a]			
Working Alliance Inventory (WAI)	X[b]						
Group Climate Questionnaire (GCQ-S)	X[b]						
Duration and Times Practicing Skills	X				X	X	X
Sleep/Wake Times	X						
Health Care Utilization			X		X	X	X
Pleasant Events Schedule SF			X		X	X	X
Behavioral Activation for Depression Scale (BADS)			X		X	X	X
Global Quality of Life			X		X	X	X
Employment Status		X	X		X	X	X
Weight		X	X		X	X	X
Mindful Awareness and Attention Scale (MAAS)			X		X	X	X
Pain Resilience Scale			X		X	X	X
Pain-Related Cognitive Process Questionnaire (PCPQ) – Full			X		X	X	X
Control, Harm, Disability, and Medication Scales from the Survey of Pain Attitudes (SOPA)			X		X	X	X
PROMIS Cognitive Function Abilities			X		X	X	X
COVID-19 Impact Questions			X		X	X	X
Treatment Credibility and Expectancies	X[c]						
Patient Global Impression of Change (PGIC)					X	X	X
Patient Global Assessment of Treatment Satisfaction (PGATS)					X	X	X
Treatment Modality & Preferences					X		
Qualitative Outcomes					X		
Optional Measures: Positive & Negative Response to Pain Scales, Future Self Questionnaire (FSQ), Valued Living Scale (VLS)			X		X	X	X

, [a] Will be assessed for each participant and reported by the clinician following every treatment session. [b] Will be assessed during the evening EMA following Sessions 4 & 8 only. [c] Will be assessed once before Session 1 and once following Session 1 but before Session 2.

D6g. Treatment Fidelity Monitoring

We will take a number of steps to ensure uniform treatment protocol delivery. First, all treatments will be provided by a Masters-level clinician, postdoctoral senior fellow, or licensed psychologist (the study "clinician") who has at least two years of clinical experience in delivering psychosocial treatments or by one of the study investigators. The clinician will be trained and supervised by the investigators who have a great deal of experience in providing the study treatments. If one of the study clinicians is unable to deliver a session as planned, and no other study clinicians are available to fill in, a clinician who has experience in delivering the treatment content may be asked to fill in during emergency situations. This emergency clinician would have documentation of training from any of the study investigators or consultants demonstrating training in the content of the session being covered. Second, the clinician will be provided with a detailed treatment manual and protocol outline. Third, Drs. Ehde (CT intervention), Day (MM intervention), or Jensen (AS intervention) will provide regularly scheduled supervision to the study clinicians. Weekly supervision will occur for the first two cohorts of every study clinician new to the program; these are anticipated to become less frequent as the clinicians gain more experience and the need for frequent supervision sessions decreases. However, all clinicians at all times will have easy access to the clinical supervisors (either in person, via telephone, via email, or via Skype) at any time between the supervisory sessions as needed and as issues arise. Fourth, adherence and fidelity will be monitored using session audio recordings. Masters-level or above clinicians supervised by the investigators will review a random selection of 25% of the recordings (2-3 randomly selected sessions per group, to be coded by the start of treatment for the following cohort) to ensure procedures are followed. Protocol quality and adherence criteria will be developed for each session with satisfactory adherence defined as ≥90% of the maximum possible score. Corrective feedback will be provided to the clinician during regularly scheduled supervision sessions; didactics and role plays to correct "drift" will be implemented if needed.

D6r. Data Collection and Management

Overview

Data will be collected at the University of Washington via telephone, online, or in person in an outpatient setting with the following two exceptions:

1. Ecological Momentary Assessment (EMA) data, which will be entered by the participant via a web portal (desktop, laptop, tablet, mobile device);
2. ActiGraph data, which will be collected via the ActiGraph device the participant will wear during participation in the study.

All study data collected for purposes of data analysis will be de-identified, labeled with a code number that is unique to each research participant, and maintained separate from any identifying information. The participant code numbers will consist of an arbitrary number consecutively numbered in order of screening/medical record review/approach. An electronic Master List key code will be maintained that links the participants with their code number. This key code along with identifying information will be stored in a password-protected Microsoft Access database that does not contain any study data. This database will also reside in a limited access folder on the UW network drive. Only approved study personnel will have access to the Master List key code, participant identifying information, and de-identified study data. We will analyze and report participant data in aggregate form and no PHI will be entered into these analyses or reports.

De-identified data collected by research staff or online will be entered directly into a database created in REDCap, a secure HIPAA-compliant web-based system. Web forms will be created to enhance functionality and proper data entry. The REDCap system also allows researchers to create an audit trail, as well as capture an e-signature from research staff attesting to the validity of the data entered. Both pieces will be utilized during data collection (i.e., we will create audit trails and require research staff to provide electronic signatures on all our electronic case report forms). Data will be downloaded to a limited access folder on the secure UW network drive.

Ecological Momentary Assessment (EMA) data will also be encrypted and stored on a HIPAA- and IRB-compliant web-based storage database. The EMA data will also be downloaded and stored in a limited access folder on the secure UW network drive.

Lastly, ActiGraph data is temporarily stored on the actual ActiGraph device until the participant returns the device to researchers. The data will then be downloaded by research staff and stored in a limited access folder on the secure UW network drive.

Recruitment and Screening

Trained study personnel will conduct the screening interview either in person or via telephone at the UW using a structured format in which the interviewer asks questions from a script. Study personnel will note the answers directly into a database if conducted via telephone or on the case report form if conducted in person. An electronic screening form as part of a REDCap database will be used to guide the screening to ensure that the same information is gathered and coded for all participants. Also, study personnel will enter basic recruitment outcome data for each prospective participant approached directly into the database using a standardized electronic case report form.

Telephone and Online Assessments

The self-report extended assessments consist of standardized protocols with specific/scripted questions. All study personnel who will be gathering data from these sources will be trained by the PIs regarding the collection of data and will have professional education and training as required by these instruments. Study personnel will enter the telephone assessment data directly into the database using a standardized electronic form in REDCap.

If the participant completes the self-report assessments online, they will be provided a secure link to a standardized electronic form in REDCap. The participant will directly complete the survey in REDCap.

EMA Data

Study participants will enter EMA data before, during, and after treatment. Study participants will be prompted via notifications to enter the data twice a day during those assessment periods. The data will be entered through a secure web portal with a link that is sent through (1) a notification on a smart phone; or (2) email, which can be accessed via desktop, laptop, tablet, or other mobile device. The data will then reside in a HIPAA- and IRB-compliant cloud-based storage database. Study personnel will check the EMA data in this database periodically to ensure participant compliance. In addition, study personnel will regularly download the data for storage in a limited access folder on the secure UW network drive.

ActiGraph Data

Activity levels will be measured before, during, and after treatment using the ActiGraph wGT3X-BT, which uses triaxial accelerometry. The participant will be instructed to wear the ActiGraph device on his/her non-dominant wrist during those periods of time. Each ActiGraph monitor will be initialized with the participant ID number for each specific participant prior to the device being sent to the participant. No identifying information is programmed into the device (although we will input the participant's study ID, planned wear location [i.e., wrist], side (right/left), height, weight, race, and sex, as reported to us by the participant). Thus, all activity and sleep data collected from participants will not contain any information that will reveal the identity of its user.

The participant will send back the ActiGraph to study personnel in a provided self-addressed stamped envelope at the end of the 4-Week Post-Treatment Monitoring Period. Study personnel will download the data collected by the ActiGraph and link it to the participant's other data via his/her participant identification number. The data will be stored in the same limited access folder on the secure UW network drive as the other data used for data analysis purposes. Data may be downloaded from the ActiGraph only with the assistance of ActiGraph software that is unavailable to the general population. That is, participants will NOT have the ability to download the data from the device itself (e.g., onto their personal computer).

Exceptions to Separation of Study Data from Identifying Information

There are four exceptions to the protocol of separating all study data from participant identifying information.

1. The group treatment sessions will be audio recorded to make sure study clinicians are following study procedures. These recordings may also be used for training purposes. The study clinicians will notify participants before the start of the session that s/he will be recording the session. The recordings will be stored in a limited access folder on the secure UW network drive. Audio recordings will be (1) reviewed by study personnel and used for assessing fidelity to treatment study procedures by study clinicians, and (2) for training purposes. The audio recordings will not be labeled with any participant identifying information. The only identifying information that will be contained in the recordings will be participants' voices and if the study clinician or group members state a participant's name during the discussion.

2. The qualitative interviews collected after the conclusion of treatment will also be audio recorded. Specifically, unblinded research staff will use open-ended questions to interview participants about their experiences in the treatment program and collect study feedback, if any. Effective 2020, there will also be a question on COVID-19's impact during treatment. Research staff will notify participants before the start of the interview that s/he will be recording the interview. The recordings will be stored in a limited access folder on the secure UW network drive. Audio recordings will be transcribed (by third party software) and reviewed and coded by unblinded study personnel only for themes that may highlight information about the program not captured by study outcome data. The audio recordings will not be labeled with any participant identifying information. The only identifying information that will be contained in the recordings will be the participant's voice and if the staff member states the participant's name during the interview. No blinded staff members will have access to these qualitative interviews.

3. Reminders/notifications to complete the EMA assessments will be sent to either a participant's email address or mobile phone number. The participant's unique ID number may be included in the reminder/notification, creating a crosswalk between the

participant's identity and participant data. Please note, however, that the EMA data that will be collected will not be stored with any identifying information.

4. Participants will be asked to complete a document outlining home practice completion. The document itself will not contain any identifying information, but since it will be on Google Drive, identifying information may be included (e.g., name or participant ID). The documents will then be downloaded from Google Drive and engagement in home practice data will be extracted and stored. The documents will be stored in a limited access folder on the secure UW network drive only accessible by unblinded research staff.

Hard Copy Data

Any hard copies of study forms will be stored on a secure, badge-protected floor in the Ninth and Jefferson Building. Any hard copy forms containing participant identifiers will be stored in locked filing cabinets in a locked cabinet separate from the de-identified study data.

Blinded/Unblinded Research Staff

The following table describes details regarding who among the study investigators and research staff will be blinded and when they will be blinded.

Staff Member	Blinded / Unblinded	When Blinded
Mark P. Jensen, Ph.D.	Unblinded (Study Co-PI, will oversee data fidelity, provide supervision to study clinicians, participate in study analysis and reporting)	N/A
Melissa Day, Ph.D.	Unblinded (Study Co-PI, will provide supervision to study clinicians, participate in study analysis and reporting)	N/A
Marcia Ciol, Ph.D.	Blinded (will help manage outcome data, design and oversee randomization procedures, primary investigator responsible for data analysis)	Blind during data collection phase of study
Dawn M. Ehde, Ph.D.	Unblinded (will provide supervision to study clinicians, help address adverse events, participate in study analysis and reporting)	N/A
Elena Mendoza, Ph.D.	Unblinded (will administer intervention)	N/A
Jennifer Altman, Ph.D.	Unblinded (will administer intervention)	N/A
Kala Phillips, Ph.D.	Unblinded (will administer intervention)	N/A
Andrea Newman, Ph.D.	Unblinded (will administer intervention, may participate in study analysis and reporting)	N/A
Calia Morais, Ph.D.	Unblinded (will administer intervention)	N/A
Janna Friedly, M.D.	Blinded (will not have access to study data or randomization assignment, may participate in study analysis and reporting)	Entire study
John Burns, Ph.D.	Blinded (will not have access to study data or randomization assignment, may participate in study analysis and reporting)	Entire study
Jeffrey Borckhardt, Ph.D.	Unblinded (will help manage unblinded data, may participate in study analysis and reporting)	N/A
Beverly Thorn, Ph.D.	Blinded (will not have access to study data or randomization assignment, may participate in study analysis and reporting)	Entire study
Joy Chan, B.S.	Blinded (will manage and collect outcome data); will not analyze or report data during data collection phase of study	Blind during data collection phase of study

Sydney Drever, B.A.	Unblinded (will manage and collect unblinded data)	N/A
Emily Stensland, B.S.	Unblinded (will help manage and collect unblinded data)	N/A
Andrea Thomas, B.S.	Unblinded (will help manage and collect unblinded data)	N/A
Madison Sherwood, B.A.	Blinded (will help manage and collect outcome data); will not analyze or report data during data collection phase of study	Blind during data collection phase of study
Shreya Pakalpati, B.A., B.S.	Blinded (will help manage and collect outcome data); will not analyze or report data during data collection phase of study	Blind during data collection phase of study
Nikki Torres, B.S.	Unblinded (will help manage and collect unblinded data)	N/A
Emily Goldberg	Blinded (will help manage and collect outcome data); will not analyze or report data during data collection phase of study	Blind during data collection phase of study
Erica Wasmund	Unblinded (will only randomize participants to treatment)	N/A
Laurel Peabody	Unblinded (will only randomize participants to treatment)	N/A

Per email discussion with the NCCIH PO on February 26, 2019, it was agreed that investigators who need to listen to treatment fidelity recordings should be listed in this protocol as unblinded to intervention (these investigators would need to listen to these recordings in order to provide supervision for study clinicians, to ensure the sessions are being conducted according to treatment protocols). These unblinded investigators will not be able to link specific participants (even if identified by name in a recording) in a given intervention to specific study data. This is because investigators do not have access to the key (a unique participant ID number) linking participant names to study data; only staff members working directly with participants will have access to this key. **To be absolutely clear, the investigators listening to fidelity recordings would not have any access to study data other than the fidelity recordings.**

At the end of the study when it comes time to conduct data analysis, study investigators (including those unblinded to intervention, such as both co-PIs) may need access to the data, in order to conduct specific analyses. Since (1) no investigators would be able to link any individual participant whose name was heard in fidelity recordings to any study data, and (2) any data investigators (blinded or unblinded) have access to at this point in the project would be locked, it is thus possible for unblinded investigators to also partake in data analysis.

Any staff member listed above may, with discretion from the co-PIs, participate in the actual writing/editing portion of any manuscript(s) that result from this study. During the data collection

phase of the study, blinded staff will not analyze or report data. Once the data is locked, all staff members, unblinded or blinded, may assist with analyzing or reporting data as needed.

D6s. Statistical Analyses

Structural equation modeling (SEM) will be used to evaluate the extent to which early treatment changes in catastrophizing, activity level, and non-judgment predict subsequent late treatment changes in pain interference, and the extent to which these associations are shared across the three treatments, or if some are unique to a subset of the treatments (Aim 1). We will also use SEM to examine the mechanisms of maintenance of gains from post-treatment to follow-up, to address the secondary study aim. Relevant covariates will be tested for and appropriately controlled for (when indicated) across all models. The Hochberg and Benjamini procedure will be used to control for alpha inflation in all analyses. This alpha control procedure involves putting the significance levels of the planned primary analyses in ascending order, and matching them to the actual significance levels obtained with the analyses, also placed in ascending order.

Specifically, we propose to evaluate mechanism effects of the three treatments using a 3-wave SEM approach[98-102]. To address Aim 1, we will calculate coefficients representing the linear change in each outcome and mechanism variable during the first two weeks of treatment (early treatment) and second two weeks of treatment (late treatment). To accomplish this, the slope of the regression line for predicting scores from the time variable will be obtained, where the Time variable consists of equally spaced fractions from 0 to 1 for each epoch (i.e., early treatment and late treatment represent two time epochs). While the majority of participants will provide many data points during these time periods, we only need two (representing just 2/24 EMA assessments, or 8% of requested data) ratings in each time period to be able to calculate the slopes for the planned analyses (see below for how any data deemed to be missing at random will be handled using this slope method). To address Aim 1, the time epochs/slopes will be operationalized/calculated as described below:

1. Pre-treatment scores: Slope calculated from EMA ratings/ActiGraph data from all available baseline data (i.e., from days 1-14, see Figure 2).
2. Early-treatment scores: Slope calculated from EMA ratings/ActiGraph data from the first day following the baseline period to mid-treatment (i.e., days 15-28, see Figure 2).
3. Late-treatment scores: Slope calculated from EMA ratings/ActiGraph data from the first day following the mid-treatment mark until the last day of the treatment period (i.e., days 29-42, see Figure 2).

To address the secondary Aim 2, we will calculate slopes from EMA and ActiGraph data across two time periods to compute scores for early and late post-treatment change for the primary outcome (pain interference) and the three mechanism variables (catastrophizing, non-judgment, and activity level), as operationalized below:

1. Early post-treatment scores: Slope calculated from EMA ratings/ActiGraph data from the first day following treatment until 2-weeks following treatment (i.e., from days 43-56, see Figure 2).
2. Late post-treatment scores: Slope calculated from EMA ratings/ActiGraph data from the first day following mid-post-treatment follow-up epoch until the end of the 4-week post-treatment period (i.e., days 57-70, see Figure 2).

Figure 2. EMA data collection and data time points used in analyses

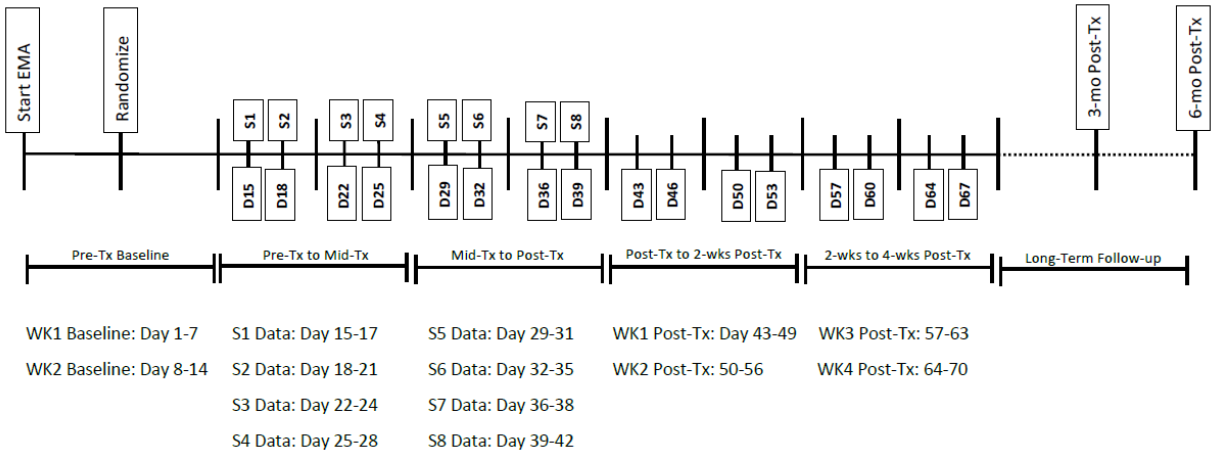
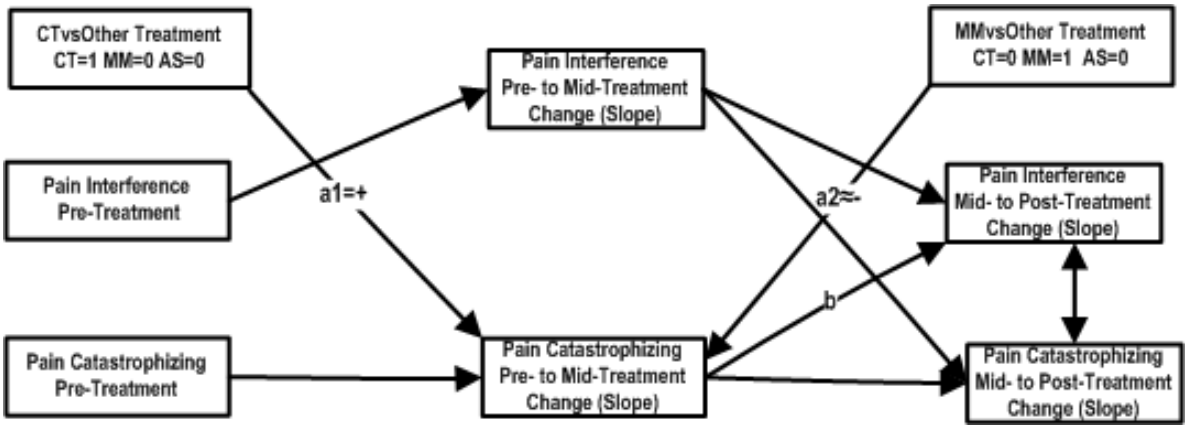


Figure 3 below represents the initial model we plan to test for the catastrophizing mechanism variable, providing that it evidences at least a small effect for change for at least one treatment condition during the first two weeks of treatment. However, the model will be simplified (by removing treatment condition as a predictor, and the paths associated with treatment condition) if non-significant treatment effects are found. Up to two additional SEM models will also be tested, with non-judgment and activity level as the foci. Below we describe the specific steps planned to address the study aims and test the primary study hypotheses.

Figure 3. Initial model testing the mechanism role of pain catastrophizing during treatment



Step 1. **Ensure at least small time effects (slope) in the early mechanism variables for at least one of the treatment conditions (a requirement for that variable to be considered as a possible mechanism).**

(1) We will perform an initial one-way Analysis of Variance (ANOVA) comparing the pre- to mid-treatment mechanism slopes between the three treatment conditions, separately for each of the three mechanism variables, with a goal of identifying the effect (i.e., Eta squared, η^2) associated with any between group differences in early changes in mechanism variable. If this effect size is < 0.01, this would indicate a less than small between-group difference in the amount of early treatment change for that mechanism;

this would be interpreted to mean that all three treatment conditions had a similar effect on early treatment change in the mechanism variable.

(2) In the event that a less than small between condition effect is found, we would then examine the pre- to mid-treatment time effect of this mechanism collapsed across groups to see if this mechanism changes from pre- to mid-treatment (i.e., early treatment). If this effect size (η^2) associated with this time effect collapsed across groups for any mechanism variable is less than 0.01 (representing a small time effect) then there would be evidence that the variable in question is unlikely to act as a mechanism, because at least some change over time early in treatment for that variable, on average, is needed for it to serve as a mechanism.

(3) If less than small effects emerge for both the between-group effects on the early mechanism slope *and* for the time effect (i.e., average slope), this would be interpreted to indicate a lack of early change (in any treatment condition) on the mechanism variable. In this instance, that mechanism variable would not be tested in a subsequent SEM. If *either* of the effect sizes are equal to or larger than 0.01 (indicating a small or larger time effect, on average) or a small or large Group X Time effect emerges (indicating at least a small group effect on early change in mechanism), then we will proceed to Step 2 for that mechanism variable.

Step 2. **Test the model presented in Figure 3 for any mechanism variable that met the Step 1 conditions described above.**

(4) First paths *a1* and *a2* will be tested. The *a1* and *a2* coefficients represent the strength of the predictive relationships from the two dummy IVs[1] to early treatment slope in catastrophizing (i.e., to evaluate the impact of treatment condition on early treatment changes in catastrophizing). Together, these tell us if treatment condition had a direct effect on the early treatment slope in the mechanism variables. If both of these coefficients are non-significant (consistent with the Shared Mechanisms Model) they will be eliminated from the final SEM. If either or both of these pathways are statistically significant, this will be interpreted to mean that there is a between-treatment condition difference in early change in the mechanism variable being evaluated, and these effects will be retained in the model.

(5) In the case of at least one statistically significant *a* coefficient, we will perform planned post-hoc ANOVA models for each of the three treatment groups to understand these differences and to determine if the findings are consistent with the Specific Mechanisms Model. For example, if catastrophizing is uniquely targeted by CT, we would anticipate a significant treatment condition effect (in either or both of the two *a* coefficients) on early catastrophizing slope, with post hoc tests indicating larger pre- to mid-treatment decreases in catastrophizing for the CT condition than the MM or AS interventions. However, the full test of the Specific Mechanisms Model also takes into account the *b* path, described below.

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[1] In the proposed SEM, treatment condition (i.e., which of three treatments the participant is assigned to) is represented by two variables: "CTvsOther" (coded as "1" if the participant is assigned to the CT condition, "0" if not) and "MMvsOther" (coded as "1" if the participant is assigned to the MM condition, "0" if not). These two dummy variables are exogenous and have a correlation of r = .50 (if groups are of equal size). When considered in the same model (i.e., when controlling for the other), the two variables contain information about all three treatment conditions.

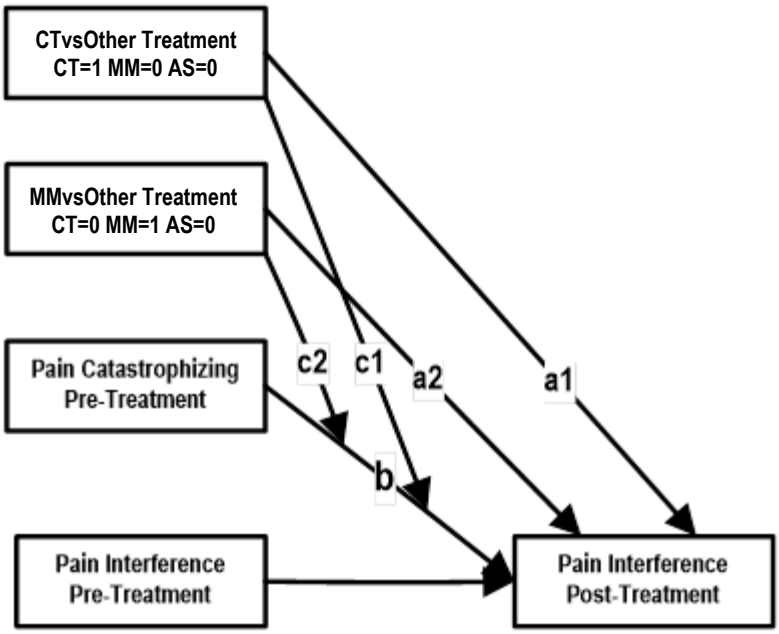
(6) In order to establish a mechanism effect on outcome (i.e., that cognitive content, cognitive process, or activity level predicts subsequent change in pain interference) we will next test for significance of the *b* coefficients. We will test the *b* coefficient for significance across each of the three mechanism variables (i.e., three significance tests, one per SEM model). Any *b* coefficients that are not significant indicate that early change in that mechanism variable is not associated with late change in pain interference, indicating a lack of support for it as a mechanism variable in treatment. A significant *b* coefficient will be interpreted as evidence supporting early treatment change in the mechanism variable in question as explaining late treatment change in pain interference.

As indicated, up to three SEMs (one for each mechanism) will evaluate and test for significance of the *a* and *b* coefficients for each mechanism variable that met the Step 1 assumptions described above (i.e., that evidenced at least a small early slope or larger, for at least one of the treatments). The combination of a treatment effect on the mechanism variable (coefficient *a*) and a significant *b* coefficient for a particular mechanism variable (indicating that early change in the mechanism variable predicts a late change in outcome), with *post hoc* tests linking each treatment to its targeted mechanism variable (i.e., CT, MM, and AS having the largest effects on cognitive content, cognitive process, and activity level, respectively) would support the Specific Mechanisms Model. A significant *b* coefficient in light of non-significant *a* coefficients (i.e., the mechanism plays a role in outcome, but all three treatments have a similar impact on the mechanism variable) would support a Shared Mechanisms Model. Thus, together, the significance levels of the *a* and *b* coefficients will address the study aims. In short, the results of the (maximum) six planned statistical tests (i.e., whether or not there are between-group differences in the three early mechanism slopes, and the significance level of the three *b* coefficients) will allow us to evaluate if the three mechanism variables play a role in treatment outcome, and whether this role is shared between the treatments or unique to a subset of them.

Exploratory Moderation Analyses

We also plan to conduct a preliminary test of the LAE model. Specifically, SEM will be used to evaluate the extent to which baseline catastrophizing, activity levels, and non-judgment are respectively associated with response to CT, AS, and MM. Figure 4 below illustrates the statistical approach that we propose to use to evaluate the LAE model. For illustrative purposes, only the role of baseline catastrophizing moderating response to treatment is depicted. As per the above models, the treatment condition variable is represented by two variables: “CTvsOther” (coded as “1” if the participant is assigned to the CT condition, “0” if not) and “MMvsOther” (coded as “1” if the participant is assigned to the MM condition, “0” if not). When considered in the same model (i.e., when controlling for the other), the two variables contain information about all three treatment conditions.

Figure 4. SEM model evaluating the “Limit” component of the LAE model



In the model depicted in Figure 4, while significant change in outcome from pre- to post-treatment is expected, it is anticipated that the effect of treatment condition on outcome will be non-significant (i.e., we anticipate that all three treatments will be associated with similar pre- to post-treatment improvements in pain interference, as reflected by non-significant *a1* and *a2* coefficients). However, the LAE model predicts that the post-treatment pain interference score, when controlling for pre-treatment pain interference, will be significantly associated with baseline levels of pain catastrophizing (i.e., path *b* in the model). We will also test the *b* coefficient for significance across each of the three moderating variables. The extent to which the effect of the baseline moderator variable predicting outcome varies as a function of treatment will then be evaluated (i.e., the *c1* and *c2* coefficients in Figure 4). These two pathways from condition to path *b* in the model, when combined and examined as a single parameter, if significant, will indicate the presence of a Treatment x Moderator interaction. In the event that this interaction effect is identified, post hoc tests will be conducted separately for each treatment condition. Continuing with the example shown in Figure 4, if baseline catastrophizing is found to be negatively associated with subsequent outcome, and this effect is stronger in CT than in MM and AS, then this will be interpreted as lending support for the predictions made with respect to the “Limit” component of the LAE model.

Additional Exploratory Analyses

We will replicate the analyses used to test Aims 1 and 2 to (1) evaluate the role of secondary mechanism variables (other mindfulness facets, pain acceptance, pain beliefs, therapeutic alliance, self-reported activity level, and client engagement) on primary outcomes and (2) the effects of the mechanism variables on secondary outcome measures (pain intensity, mood, physical functioning, sleep quality, morphine equivalent, health care use). We will also examine longer (macro) follow-up mechanism effects using the 3- and 6-month follow-up data. Specifically, we will perform a further three-wave SEM model (as described above) to determine if post-treatment to 3-month follow-up changes in the primary and secondary mechanism variables predict subsequent 3-month to 6-month changes in the primary and secondary outcomes. We will also explore the potential role of participants’ emotional responses to COVID-19 in relation to outcome and tests of mechanism.

Finally, we plan to conduct Simulation Modeling Analysis (SMA) of the EMA and ActiGraph data to examine the time course of change (i.e., trajectories over time) in cognitive content, process, and activity level during treatment and post-treatment, and whether these trajectories differ between treatments[103-106]. SMA permits time-series analyses and cross-lag correlational analyses (while controlling for type-I error inflation associated with autocorrelation) without the need for deconstructing the variables via partialling-out autoregressive elements. Thus, we will be able to model the variables of interest in their raw and most meaningful (ecologically valid) form as opposed to traditional time-series analytic techniques that examine the residuals of auto-regressive fitted models. For each participant, we will determine: (1) which of the mechanism variables changed significantly during treatment; (2) for any that changed, when during treatment the change occurred; (3) whether a significant change in mechanism predicted a subsequent change in the primary and secondary outcomes (e.g., if a decrease in catastrophizing preceded a subsequent decrease in pain interference); and (4) how long the effect on the outcome (lag time, in days) took to occur. The results of these analyses will provide important descriptive information regarding the importance and effects of the mechanisms at the individual person level; findings which can then be used to determine which mechanism to target first with treatment (i.e., if increases in non-judgmental awareness precede decreases in pain interference for 90% of the participants, while decreases in catastrophizing precede decreases in pain interference for 60% of the participants and increases in ActiGraph-assessed activity level precede decreases in pain interference 20% of the time, this would suggest that to have the most effect on pain interference, individuals would do well to first learn and practice mindfulness meditation over making changes in the other mechanisms). All of the exploratory analyses will be presented as such (i.e., as exploratory, and in need of confirmation in additional studies) in all papers and presentations.

D6t. Missing Data

Because it is likely that we will encounter at least some missing data despite procedural efforts by research staff to minimize its occurrence, we have attempted to further address missing data in a number of ways via our data analysis approach. First, we will examine potential patterns of missing data that represent confounds contributing to biased slopes. So, for each participant, analyses to identify potential patterns in missing data will be conducted to determine if they are “ignorable” (see Schafer & Grahem, 2002)[107]. If >5% of the participants do not provide adequate data, the sample will be divided into two groups (missing data, no missing data) and fully observed variables will be examined to determine if they significantly predict missingness on the affected outcome. This test will be done on a variable-by-variable basis. If this analysis is non-significant, the missingness will be considered “observed at random” and the procedures described below for calculation of slope coefficients in the instance of missing data will be used, without necessitating the use of multiple imputation procedures. However, if no data is available to calculate slope via the below methods, in Mplus, the missing data (slopes and estimated end values from slopes) are treated automatically (by default) by estimating the full model from available data using full information maximum likelihood (FIML). The Mplus robust maximum likelihood (MLR) estimator using FIML permits missing completely at random (MCAR) and missing at random (MAR), and MLR uses SEs that are corrected for non-normality and also uses a corrected chi-square fit statistic. If data missingness is not ignorable, Heckman’s selectivity models of pattern-mixture models with multiple imputation will be used to model the “missingness" for each participant before calculation of slopes from the daily EMA and ActiGraph data.

There are several ways to treat data that are deemed to be missing at random (from the daily EMA and ActiGraph data) using the slope method. For example, consider the six cases below (from real data). The dependent variable was measured at five equally spaced intervals within the epoch. Within the current study, there are additionally two observations per day, and we propose to calculate the slopes from morning and evening observations, and to average those slopes.

Cases	0	0.25	0.5	0.75	1	Slope	Difference
1	12	14	15	15	10	-1.2	-2
2	12	10	11	10	7	-4	-5
3	23	19	13	13	12	-11.2	-11
4	15	16	12	13	8	-6.8	-7
5	29	21				-32	
6	21	22	15	20	12	-8	-9

In the above example, for Case 5, the slope is estimated to be -32, because it is based on the first two Time points, where there is a substantial decline. The decline is magnified by extrapolating the line over the full time period, and the score is probably an outlier. Hence, there are weaknesses to the slope method. However, one approach is to carry the last observation forward and first observation backward when there are missing data at the beginning or end of an epoch. The difference for Case 5 would then be -8 and the slope would be -6.15. Given there are four epochs in the current study, this method becomes somewhat complicated. However, we propose to carry forward or carry backward the closest score in the full sequence of scores from the beginning of pre-test to the end of post-test.

D6u. Power Analyses

We will conduct ***six primary*** statistical tests to test the primary aim for three mechanism variables, in order to better understand the effects of the treatments on pain interference. Data from prior research – including means and standard deviations – was used to support the anticipated medium to strong effects of the mechanism paths that we propose to test, and which form the basis of our assumptions for the power analyses.

With respect to the effects of treatment on the primary outcome variable – in a recent meta-analysis by Veehof et al.[108], the effect of **mindfulness meditation** (MM) interventions on pain interference was examined across four separate studies. A moderate effect-size (standard mean difference) was observed for MM interventions on pain interference (effect-size = 0.51; 95% confidence interval 0.21-1.03) justifying our mediated-effect-pathway (path *a*) assumptions(s) of small to medium magnitude. With respect to the **activation skills** (AS) intervention component of our proposal, Plagge et al.[109] observed pre- to post-intervention pain interference scores of 6.9 [SD = 2.1] to 4.9 [SD = 2.5] in n=30 AS treatment-completers, yielding a large Cohen's *d* effect-size of 0.87. Thus, we believe that our estimate of a moderate to large mediated-effect-pathway (path *a*) effect-size is appropriate and leaves us well-powered given the proposed n-size(s). Lastly, in a recent study conducted by the investigators on the current proposal regarding the unique effects of **cognitive therapy** (CT) on pain interference (the only study we are aware of to date), we observed pre- to post-intervention pain interference scores of 4.31 [SD=2.00] and 3.26 [SD=2.09], respectively in 40 patients. Thus, the effect-size for this specific intervention (Cohen's *d* = 0.51; medium) also supports our power assumptions with respect to the effects of the treatments on the primary outcome.

With respect to the causal effects of the treatments on the mechanism variables – data are available regarding the effects of treatment on catastrophizing and mindfulness. For example, a paper reporting the results of a study from one of the PIs of the current proposal found a large effect for MM on catastrophizing (pre-treatment mean [SD] = 19.44 [10.81], post-treatment mean [SD] = 10.22 [9.87]; Cohen's *d* = 0.89)[110]. Plagge et al.[109] reported large effects for an AS treatment on a measure of catastrophizing (pre-treatment mean [SD] = 32.9 [13.0], post-treatment mean [SD] = 23.9 [10.5]; Cohen's *d* = 0.76). In a just-completed study, referred to in the previous paragraph, we found large pre- to post-treatment decreases in catastrophizing in participants with chronic pain who received 4 sessions of CT (pre-treatment mean [SD] = 19.38 [10.90], post-treatment mean [SD] = 12.99 [9.76]; Cohen's *d* = 0.62). In a recently published study by Turner et al.[111], significant improvement in facets of mindfulness were observed for both a cognitive-behavioral treatment and a mindfulness intervention as compared to the usual care control. Although we were unable to identify any studies that examined the effect sizes associated with any of these treatments on behavioral activity (discovering this will be one of the valuable outcomes of the current proposal), as a group these studies are consistent with our assumptions that MM, AS, and CT treatments have medium to strong effects on key mechanism variables.

With respect to the association between mechanism variables and pain interference, there is a great deal of research reporting strong associations between catastrophizing and pain interference. Consistent with these data, in our recently completed study examining the effects of four psychosocial treatments on pain interference from the same study mentioned previously, the association between pre- to post-treatment change in catastrophizing and change in pain interference was *r* = 0.57 (note: for the *r* statistic, this represents a large effect). Two published articles present the association between measures of mindfulness and pain interference.[112,113] These associations (*r*s = -0.30 and -0.35) were both in the medium range. Again, these findings are consistent with our assumptions that mechanism variables can evidence at least medium effects with pain interference.

Assuming at least medium effects (i.e., *r*s ≥ .30 and/or *d*s ≥ .50), we can then compute the sample sizes needed to detect significant effects for the planned primary analyses, using the Hochberg and Benjamini procedure to control for alpha inflation in these analyses. This alpha control procedure involves putting the significance levels of the six planned primary analyses in ascending order, and matching them to the actual significance levels obtained with the six analyses, also placed in ascending order. The number needed to detect significant effects for each of these analyses is presented in Table 5, below, using the tests for the three direct mediation effects of the mechanism variables for three of these analyses, and a test for the three Treatment Condition X Mediation (representing moderated mediation) effects for the other three analyses, assuming at least medium effects for each of these effects. Sample size estimates needed to detect the primary mediation effects were conducted based on the joint significance method of testing mediated effects, using the PowMedR program in R Version 3.0.2 statistical software with the following assumptions: (1) alpha levels consistent with the Hochberg and Benjamini procedure (see Table 5, below); (2) power of 0.80; and (3) at least medium effects. Power calculations for the interaction (mediated moderation) analyses were conducted using G*Power3 with the same assumptions.

Table 5. Sample size estimates for the six planned analyses, assuming medium effects for the causal paths (a and b) and at least a medium interaction effect (f^2) for the three planned Treatment Condition X Mediation effects tests

Alpha	Power	Effect size path a	Effect size path b	Interaction effects	n-required / n-planned
0.050	0.80	Medium (***r*** = 0.30)	Medium (***r*** = 0.30)		109 / 240
0.025	0.80	Medium (***r*** = 0.30)	Medium (***r*** = 0.30)		129 / 240
0.017	0.80	Medium (***r*** = 0.30)	Medium (***r*** = 0.30)		140 / 240
0.013	0.80			Medium (***f²*** = 0.15)	93 / 240
0.010	0.80			Medium (***f²*** = 0.15)	98 / 240
0.008	0.80			Medium (***f²*** = 0.15)	102 / 240

Thus, by employing the analytic models experiment-wise, and by integrating treatment-condition into the model(s) as an interaction effect (rather than running separate analyses for each treatment condition), we will be able to take advantage of the power afforded by running the entire sample of participants (n = 240) through the planned tests. This, combined with the less stringent Hochberg and Benjamini type-I error adjustment (alpha-correction), has left us well-powered to detect the hypothesized effects. That said, we plan to enroll 300 participants with a goal of obtaining complete data for 240 participants (n = 80 per condition) to ensure that we will be able to compute reliable effect sizes for the planned secondary analyses (the results of which will be discussed in terms of their effect sizes and not significance levels, although significance levels and associated confidence intervals will also be reported).

HUMAN PARTICIPANTS SECTION

E. Risk to Participants

E1. Human Participants Involvement and Characteristics

We plan to enroll up to 300 participants into the study. Our primary source of potential participants for this study is all individuals who have been seen as patients at either Harborview Medical Center (HMC) or the University of Washington Medical Center (UWMC), and who meet study eligibility criteria.

If needed and required, we will also recruit from other modalities. These other modalities include through flyers/brochures/advertisements in various clinics and hospital spaces, the UW Medicine Newsroom, clinician and participant referrals, social media/online recruitment, and nationally, if needed.

E2. Sources of Materials

Several sources of information will serve as data for the study, including medical record reviews, self-report assessments and interviews, ActiGraph activity data, and audio-recorded treatment sessions (to be used for supervision and determination of adherence and fidelity). The study design involves non-invasive procedures.

The data described will be collected solely for research purposes.

E3. Potential Risks

It is anticipated that participants, irrespective of treatment condition, will experience significantly more benefits than risks from participation in this study. Although the methods and interventions have limited participant risks, several safeguards will be implemented to reduce these.

E3a. General / Reaction to Assessments

Regarding research risks, participants may experience fatigue and/or boredom while completing the telephone/online assessments, EMA surveys, and/or the treatment sessions. Some participants may also experience mild anxiety, frustration, and/or stress while answering sensitive questions about depression, pain, and mood. As a result of answering questions about pain, some participants may focus more on their pain, which may lead to a temporary increase in pain intensity. Participants will be told that such phenomena associated with close self-monitoring are a part of the treatment approaches we are offering, and will be addressed as part of the interventions.

E3b. Stress / Discomfort Caused by Treatments

Our research team has had a great deal of experience with each of the treatments to be examined in this study, and each has minimal risks. The three types of treatment involve discussions about pain and related topics in a group setting that may make some individuals feel uncomfortable. Some participants may also experience mild anxiety, frustration, and/or

stress during the course of treatment should any topics or activities prove difficult for them. Some individuals learning cognitive restructuring of thoughts and beliefs or practicing mindfulness meditation may remember past experiences that are uncomfortable and/or cause distress, even after the session has ended. Regarding the mindfulness meditation training, some individuals may find the state of focused awareness uncomfortable, or may experience mild disorientation or grogginess during or after the session has ended due to the occasionally relaxing nature of this practice. Regarding the activation skills intervention, although clinicians will instruct participants engage only in safe and personally appropriate activities, there is a risk that participants may experience physical strain or injury when conducting activities with a physical component.

Should any participants experience these discomforts, the intervention leaders are clinicians with the expertise and clinical privileges needed to address these in appropriate clinical fashion in real time. Study investigators (Drs. Jensen, Ehde, and Friedly) are also available on site for additional consultation or support if needed. There is little chance of physical injury from the treatment procedures described above.

One potential risk is that participants may experience some distress when sharing personal information during the group telehealth intervention, although this is a relatively low risk event, because personal disclosure will not be specifically elicited. To reduce distress about public disclosure, the meaning of confidentiality will be explained at the outset of each session and group members will be asked to maintain the confidentiality of all session content. Participants will be explicitly instructed that revealing deeply personal information, by exploring the past or confiding in the group about personal information, is not considered part of the treatment protocol. Additionally, any participant expressing significant discomfort in the group treatment will be referred for alternative treatments. Participants may also feel uncomfortable because the sessions will be audio-recorded. Participants who choose to participate in the intervention will be advised at the time of informed consent that sessions will be audio recorded, so that they may self-select out of the study if recording is a barrier. Participants will be informed that the session recordings will be used only for treatment implementation monitoring and training purposes, and that no one outside the study staff will have access to the recordings.

E3c. Actigraphy Device

Participants may find it uncomfortable or inconvenient in general to wear a device like an ActiGraph both during the day and while sleeping. There is no risk of electrical shock while wearing the ActiGraph and it cannot track where participants are, record any verbal/audio, or track what behavior they are specifically doing. Participants may experience sweating or skin irritation while wearing the ActiGraph if they have sensitive skin.

E3d. Privacy and Confidentiality

Participants may also worry about the confidentiality of their responses during the assessments. There is a risk of invasion of privacy in that the research staff directly involved with data collection will need to keep participants' names, addresses (email and postal), and phone numbers for the duration of the study in order to contact them for the follow-up assessments. There is also a chance that a participant's identity and participation in the study may be discovered by an outside party given the group intervention dynamic. Given that this is a group intervention, participants within each group will know the first names and some information about other participants. However, participants will be encouraged to share only

their first names, and to disclose only that information that they are comfortable sharing and that pertains to pain and treatment.

E3e. Mental Health Issues / Suicidality

Although unlikely, it is possible that by participating in the study it may be discovered that a participant is suicidal or experiencing significant mental health issues. Please note that these conditions would also likely be detected in the course of usual care. The study suicide protocol will be implemented in the instance of a participant expressing suicidality.

E4. Protection Against Risk

E4a. General / Reaction to Assessments

Participants will be informed during the consent process and throughout the study they do not have to discuss any topics they do not wish to during treatment or the assessment periods. In addition, participants will be informed in the consent process they are free to stop any session, treatment, or assessment at any time. Participants are informed they may refuse to answer any questions that make them feel uncomfortable.

All study personnel who conduct the assessments will be qualified, trained, and closely supervised by study investigators. All participants will be clearly informed of their right to withdraw from the study at any point without adversely impacting their routine medical, psychiatric, or psychotherapeutic care.

All participants will be offered the opportunity to discuss any situations or experiences associated with the study procedures that they deem uncomfortable or adverse with the UW Co-PI, Dr. Jensen, who is a licensed clinical psychologist. Dr. Jensen is a trained psychologist who has experience assessing the level of distress of patients and proceeding accordingly whenever an adverse event should arise.

E4b. Stress / Discomfort Caused by Treatments

Researchers will take multiple steps to ensure and monitor the well-being of participants during treatment. Study investigators, led by Dr. Ehde, will offer ongoing, scheduled supervision and consultation with study clinicians, including routine assessment of any potential problems or adverse events.

Regarding the activation skills intervention, several steps will be taken to ensure participants do not incur physical injury. First, during the recruitment process, research staff will clearly outline the physical components of the activation skills intervention. In doing so, staff will also instruct individuals who are concerned about the physical nature of the intervention to consult their physician before agreeing to participate.

Secondly, clinicians will employ several protective measures when administering the activation skills intervention. At the first treatment session, clinicians will get to know the personal physical capabilities of each participant, allowing any future physical activity recommendations to be tailored to the individual. Further, before participants complete any

assigned physical activities, the clinician will review the activity with the participant to ensure that it is reasonable and safe.

E4c. Actigraphy Device

Participants will be warned about possible irritation to the skin and general discomfort wearing the device during the informed consent session. If the participant says s/he cannot wear the ActiGraph due to skin irritation, researchers will provide the participant with a more comfortable way of wearing the ActiGraph on the wrist (e.g., using a softer material on the wrist strip).

E4d. Privacy and Confidentiality

We will take multiple steps to protect participants' privacy and confidentiality. All of the data collected from participants will be kept in strict confidence. No information that is linked to a research participant's identity will be provided to anyone outside of the study or regulatory entities responsible for oversight without permission from the participant.

Electronic Data

All study data collected for purposes of data analysis will be de-identified, labeled with a code number that is unique to each research participant, and maintained separate from any identifying information.

All electronic data collected via telephone, online, and Ecological Momentary Assessment (EMA) data will be encrypted and stored in a HIPAA- and IRB-compliant web-based system. These data will also be downloaded and saved in a limited access folder on the secure UW network drive.

The participant will send back the ActiGraph to study personnel in a provided self-addressed stamped envelope at the end of the 4-Week Post-Treatment Monitoring Period. Study personnel will download the data collected by the ActiGraph and link it to the participant's other data via his/her participant identification number. The data will be stored in the same limited access folder on the secure UW network drive as the other data used for data analysis purposes. Data may be downloaded from the ActiGraph only with the assistance of ActiGraph software that is unavailable to the general population. That is, participants will NOT have the ability to download the data from the device itself (e.g., onto their personal computer).

An electronic Master List key code will be maintained that links the participants with their code number. This key code will be stored in a password-protected Microsoft Access database that does not contain any study data. This database will also reside in a limited access folder on the UW network drive. Only approved study personnel will have access to the Master List key code, participant identifying information, and de-identified study data. We will analyze and report participant data in aggregate form and no PHI will be entered into these analyses or reports.

One exception to the protocol of separating all study data from participant identifying information pertains to audio recordings generated for each treatment session. Specifically, the group treatment sessions will be audio recorded to make sure study clinicians are following study procedures. The study clinicians will notify participants before the start of the session that s/he will be recording the session. The recordings will be stored in a limited access folder on the

secure UW network drive. Audio recordings will be (1) reviewed by study personnel and used for assessing fidelity to treatment protocol by study clinicians, and (2) used for training purposes. The audio recordings will not be labeled with any participant identifying information. The only identifying information that will be contained in the recordings will be participants' voices and if the study clinician or group members state participants' names during the discussion.

Another exception pertains to the audio recorded qualitative interviews collected after the conclusion of treatment. Specifically, unblinded research staff will use open-ended questions to interview participants about their experiences in the treatment program and collect study feedback, if any. Effective 2020, there will also be a question on COVID-19's impact during treatment. Research staff will notify participants before the start of the interview that s/he will be recording the interview. The recordings will be stored in a limited access folder on the secure UW network drive. Audio recordings will be transcribed (by third party software) and reviewed by unblinded study personnel only and coded for themes that may highlight information about the program not captured by study outcome data. The audio recordings will not be labeled with any participant identifying information. The only identifying information that will be contained in the recordings will be the participant's voice and if the staff member states the participant's name during the interview. No blinded staff members will have access to these qualitative interviews.

Additionally, another exception is the alerts sent to participants to complete the EMA surveys via notifications and/or email messages. Specifically, the alert may include the participant's identification number in the body of the notification/email, creating a crosswalk between the participant's identity and participant data. Please note, however, that the EMA data that will be collected will not be stored with any identifying information.

Finally, participants will be asked to complete a document outlining home practice completion. The document itself will not contain any identifying information, but since it will be on Google Drive, identifying information may be included (e.g., name or participant ID). The documents will then be downloaded from Google Drive and engagement in home practice data will be extracted and stored. The documents will be stored in a limited access folder on the secure UW network drive only accessible by unblinded research staff.

Hard Copy Data

Any hard copies of study forms will be stored on a secure, badge-protected floor in the Ninth and Jefferson Building. Any hard copy forms containing participant identifiers will be stored in locked filing cabinets in a locked cabinet separate from the de-identified study data.

E4e. Mental Health Issues / Suicidality

Although the study poses no serious risks to participants, participants may notify research personnel about pre-existing mental health issues that have not been previously identified. A suicide risk assessment protocol will be implemented by non-clinical staff (see below). It should be noted that risk of suicide is an exclusion criteria for this study, so we anticipate that the likelihood of suicide risk is low.

Suicide Risk Assessment Protocol: Non-Clinical Research Staff

A suicide risk assessment protocol will be implemented by non-clinical staff under the following condition:

If a participant mentions or alludes to thoughts, intentions, plans or behaviors related to self-directed violence (SDV) outside of the context of formal assessment.

Study staff (e.g., Research Coordinator, Research Assistant) are not licensed mental health providers. This protocol outlines specific steps that study staff will follow in order to ascertain whether a study investigator or study clinician who is supervised by a licensed mental health care provider needs to be contacted for follow-up assessment and/or triage. In the event that a study staff member perceives sufficient risk that further assessment is warranted, the study staff will alert an investigator or a study clinician who can assess risk. Because our research staff are not clinicians (i.e., they have no official clinical role), our plan primarily reflects the importance of *activating the procedures for suicide risk assessment and risk management/suicide prevention.*

Thus, in the event that the participant mentions thoughts, intentions, or plans related to harm to self, the research staff member will ask the participant some clarifying questions, such as: "Let me clarify, are you having any thoughts about harming yourself deliberately, or are you just thinking about dying or that you would be better off dead?" or "Let me clarify, are you having any thoughts about deliberately harming yourself?" If the participant endorses follow-up questions that suggest a possibility of risk for suicide, the research staff member will gather additional information about acute risk (i.e., presence of intent, plan, means for self-directed violence, protective factors such as presence of dependents).

In the course of this discussion, if the participant clarifies that while they are having thoughts about self-harm, they have no intent or plan, and if they volunteer reasons they would not harm themselves (e.g., having dependents, or religious beliefs that prevent suicide), then this will be considered a negative screen. Because suicide risk assessment for clinician is beyond the role of non-clinical research staff members, we propose a low threshold for a positive screen.

1. In the event of a negative screen, the research staff member will complete the interaction with the participant, and then alert Dr. Jensen, Dr. Ehde, or a study clinician within 24 hours to review the screen and determine if further action needs to be taken.

2. In the event of a positive screen over the telephone during an assessment (i.e., if the research staff member perceives that there is imminent risk of self-harm because the participant has expressed information about intent, means, plans for self-harm) then the research staff member will:

    a. Verify the contact information and location of the participant and thank them for their candor and advise the participant that they will be contacting a mental health provider to perform a further assessment. They will use the following script: "Thank you for being honest with your answer(s). To ensure that you are safe and getting any help you might need I am going to ask a mental health provider to speak with you more about this." The research staff member will keep the participant on the phone while using another modality of communication (i.e., text, e-mail, pager) to reach Dr. Jensen, Dr. Ehde, or a study clinician who is supervised by Dr. Jensen or Dr. Ehde (who are both licensed, privileged, and credentialed) to do more in-depth assessment of risk.

    b. Once a clinician contacts the participant they will follow best clinical practice for the assessment and management of suicide risk (see "Suicide Risk Reduction Protocol – Clinical Staff" below).

c. If a clinician is not available immediately and/or if the research staff member perceives imminent risk, they will encourage the participant to seek immediate evaluation at the nearest ER and/or to contact the National Suicide Prevention Lifeline (https://suicidepreventionlifeline.org/).

d. After directing the participant to the crisis line or ER, the research staff member will follow-up with Dr. Jensen or Dr. Ehde to determine if additional steps (e.g., calling 911) need to be taken. A study clinician will follow up with the participant within 24 hours.

e. Dr. Jensen, Dr. Ehde, or a study clinician who is supervised by a licensed health care provider will document actions taken. An AE report will also be filed if indicated.

3. In the event that a study staff member has reason to believe a participant is in grave danger (as would be the case extremely rarely, and only if they made explicit statements to this effect):

   a. The staff member could contact local police and request a well-being check.

Suicide Risk Assessment Protocol: Clinical Research Staff

The goal of this protocol is to ensure that reasonable steps are consistently taken by study clinicians and investigators to protect participant safety and welfare. The study clinicians will be credentialed and privileged providers at the UW or Masters-level or post-doctoral level clinicians under the supervision of a credentialed and privileged UW provider. Additionally, both Dr. Jensen and Dr. Ehde are credentialed, privileged, and licensed providers at the UW. Should there be any indication of risk for self-directed violence that arise during interactions with study staff, the study clinicians/investigators will follow the same specific procedures and policies that psychologists who are clinicians at UW follow for assessing and managing risk.

In instances where the clinician is concerned about safety/suicide risk in a study participant (i.e., if they state or allude to thoughts or plans of self-directed violence, mention recent self-directed violent behavior or behavior preparatory to self-directed violence during a study intervention session), or in instances where a study clinician/investigator is contacted by a research staff member and asked to follow-up with a participant, the study clinicians/investigators will follow the same risk assessment and prevention protocol that is required of UW licensed psychologists.

F. Data Safety Monitoring

F1. Adverse Event & Unanticipated Problems Definitions

F1a. Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a participant during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study. Staff will document any occurrence that meets this definition, is a new symptom/condition for the participant, and results in either self-treatment or treatment by a health care provider.

F1b. Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

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

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

F1c. Serious Adverse Event (SAE)

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death;

- Is life-threatening (places the participant at immediate risk of death from the event as it occurred);

- Results in inpatient hospitalization or prolongation of existing hospitalization;

- Results in a persistent or significant disability or incapacity; or

- Results in a congenital anomaly or birth defect.

An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment,

the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

F2. Characteristics of an Adverse Event

F2a. Relationship to Study Procedures

To assess relationship of an event to the study procedures, the following guidelines are used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the particular study procedure.
    b. There is a temporal relationship between the study procedure and event onset.
    c. The event abates when the study procedure is discontinued.
    d. The event reappears upon re-introduction of the study procedure.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the study procedure and event onset.
    b. An alternate etiology has been established.

F2b. Expectedness of SAEs

The Study PIs will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedure.

F2c. Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; participant seeks medical attention, needs major assistance with ADL
4. Life-threatening: the event is potentially fatal

F3. Reporting Procedures

F3a. Regulatory Event Documentation

All regulatory events, incidents, or problems involving risks to participants, including AEs, SAEs, and Unanticipated Problems (UP), will be documented in the REDCap electronic database that houses all study data. All regulatory events will share a common electronic form template. Two separate copies of the same form will exist, (1) one for events involving information that could unblind staff to a participant's treatment allocation, and (2) another for events without details that could unblind staff to a participant's treatment allocation. Only unblinded staff will have access to the form that outlines events with details that could unblind staff to a participant's treatment intervention. The form will be filled out for every regulatory event. A study clinician will review all events that are designated AEs or SAEs to assess severity and relationship to study procedures.

The Regulatory Event form will assess the following information for all three event types (AE, SAE, and UP):

- A brief description of the incident/problem.
- Dates corresponding to event onset, stop, and location.
- Whether or not the event was unexpected or unanticipated.
- Whether or not the event placed participants or others at greater risk of harm than was previously recognized.
- The degree to which the event was related to study procedures.
- Whether or not the study procedures were discontinued due to the event.
- The steps taken to remedy the event.
- The steps taken to report the event to the appropriate entities.
- (AE/SAE only) A ranking of the severity of the event according to section F2c.
- (AE/SAE only) The specific outcome of the event.
- (SAE only) The category of the SAE.

For reporting purposes, regulatory event documentation will be aggregated into central reports using REDCap's "Reports" functionality. The "Reports" functionality allows data to be pulled from the Regulatory Event forms and summarized in one central report. The content of these reports and the frequency in which they are distributed to regulatory bodies is outlined in sections F3b. and F3c.

F3b. AE Reporting

Research staff will generate reports summarizing all AEs for each participant using the REDCap "Report" feature outlined above in section F3a. The report will contain the participant's code number, date of AE, severity, attribution level to study, action taken, and outcome. These

adverse events will be provided quarterly in this format to the DSMC, UW IRB, and NCCIH in accordance with requirements.

F3c. SAE/Unanticipated Problem Reporting

- Unanticipated fatal or life-threatening SAEs at least possibly related to study procedures will be reported immediately to the NCCIH Program Officer, Chair of the DSMC, and the UW IRB.

- Breaches of confidentiality or inappropriate access to protected health information will be reported to the NCCIH Program Officer, Chair of the DSMC, and the UW IRB within 24 hours.

- Other unanticipated SAEs or serious problems at least possibly related to study procedures will be reported to the NCCIH Program Officer and DSMC Chair within 5 days, and to the UW IRB within 10 days.

- Anticipated or unrelated SAEs will be reported to the DSMC and NCCIH Program Officer as part of the annual DSM report.

Research staff will record all SAEs and unanticipated problems using the Regulatory Event form outlined above in section F3a. These serious adverse events/problems will be summarized using the REDCap "Report" format and provided quarterly in this format to the DSMC, the UW IRB, and NCCIH in accordance with requirements.

The Chair of the DSMC will be contacted when an SAE/unanticipated problem is discovered to receive consultation on the matter. The Chair of the DSMC will use her discretion to determine whether the other DSMC members should also provide additional consultation.

F4. Data Quality and Safety Review Plan and Monitoring

F4a. Description of Plan for Data Quality and Management

Data collected by research staff will be entered directly into a database created in REDCap, a secure HIPAA-compliant web-based system. Web forms will be created to enhance functionality and proper data entry. The REDCap system also allows researchers to create an audit trail, as well as capture an e-signature from research staff attesting to the validity of the data entered (in instances where an e-signature is specified).

All group treatment sessions will be audio recorded to ensure compliance to treatment procedures. These recordings may also be used for training purposes. A portion of treatment sessions will be randomly selected to be reviewed by study researchers to ascertain fidelity to protocol. Study clinicians will receive feedback as needed if they diverge from protocol.

In addition, research study staff will review the study data in detail on a quarterly basis to detect any systematic issues with data collection and protocol compliance. Data types that will be reviewed include participant accrual, status of enrolled participants, adherence data regarding study assessments and intervention, any protocol deviation or violation that warrants a note-to-file, and AEs, SAEs, and unanticipated problems.

Regarding protocol deviations, only participant study visits completed outside of the protocol-defined windows would be considered protocol deviations; non-completion of study components by participants would not result in protocol deviations. This was approved by the NCCIH PO on 5/25/2018.

F4b. Frequency of Data Review

The frequency of data review for this study differs according to the type of data and can be summarized in the following table:

Data type	Frequency of review	Reviewer
Participant accrual	Quarterly	Co-PIs, Chair of DSMC
Status of all enrolled participants	Quarterly	Co-PIs, Chair of DSMC
Participant adherence to study procedures	Quarterly	Co-PIs, Chair of DSMC
AEs	Quarterly	Co-PIs, Chair of DSMC
SAEs	Per occurrence	Co-PIs, Chair of DSMC, NCCIH, UW IRB
Unanticipated Serious Problems	Per occurrence	Co-PIs, Chair of DSMC, NCCIH, UW IRB

F4c. Participant Accrual and Compliance

Review of the rate of participant accrual and compliance with inclusion/exclusion criteria will occur monthly during the first six months of recruitment and then every three months to ensure that a sufficient number of participants are being enrolled to allow for an adequate test of the primary study hypotheses and that they meet eligibility criteria.

F4d. Measurement and Reporting of Participant Adherence to Treatment Protocol

Data on participant adherence to the study protocol will be collected monthly by research staff and reviewed quarterly by the PI and the Chair of the DSMC. Adherence of participants to both assessment completion and treatment will be evaluated by running queries to discern adherence rates. If adherence falls below the rate of 80% for EMA assessments or 85% for non-EMA pre- and post-treatment assessments, which might put at risk the ability to test the study's primary hypotheses, the Chair of the DSMC will suggest a conference call for study investigators to discuss methods for improving adherence.

F4e. Stopping Rules

This study will be stopped prior to its completion if: (1) one of the interventions is associated with adverse effects that call into question the safety of the intervention; (2) any new information becomes available during the trial that necessitates stopping the trial; or (3) other situations occur that might warrant stopping the trial.

F4f. Designation of a Monitoring Committee

Name/Role	Credentials	Organization	Expertise
Mary Beth Brown / Chair	P.T., Ph.D.	UW	Physical Therapist, conducts research on exercise therapy in cardiopulmonary populations
Tracy Jirikowic	Ph.D., OTR/L, FAOTA	UW	Occupational Therapist, conducts health services research (including clinical trials) on individuals with disabilities
Katie Odem-Davis	Ph.D.	Independent Consultant	Biostatistician
Sean Rundell	P.T., Ph.D., D.P.T.	UW	Physical Therapist, conducts health services research with focus on low back pain

The Data Safety Monitoring Committee (DSMC) for this study is comprised of Drs. Brown, Jirikowic, Odem-Davis, and Rundell.

Dr. Brown is qualified to chair the DSMC because of her expertise in the area of exercise science research and randomized controlled trials. Dr. Jirikowic is qualified to review the patient safety data generated by this study because of her expertise in the area of rehabilitation research and randomized controlled trials. Dr. Rundell has considerable experience conducting health services research with a focus on low back pain. Dr. Odem-Davis was selected given her expertise in biostatistics.

F4g. Safety Review Plan

Study researchers, including staff members and study clinicians who conduct the telephone assessments and facilitate the treatment groups, will collect safety information on an ongoing basis. By systematically monitoring for events, we will ensure that problems are detected immediately and addressed as indicated.

Treatment

Study clinicians will collect unsolicited information reported by participants during treatment sessions including, but not limited to, physical or psychological decline, or unexpected reactions to the treatment intervention.

Any AEs collected during treatment sessions will be recorded on the participant's REDCap Regulatory Events form created and completed during participation.

General

Research staff and study clinicians will collect unsolicited information reported by participants during study participation including suicidal thoughts or suicidal ideation (SI), increased alcohol/drug use, intentions to harm someone else, or psychological decline.

Any AEs collected during the course of the study will be recorded on the participant's REDCap Regulatory Events form created and completed during participation.

All information leading to an adverse event (AE), serious adverse event (SAE), or unanticipated problem (UP) will be reported per UW protocol/requirement, i.e., to UW IRB using the approved UW IRB forms. All documentation collected, submitted, and approved will be stored in a regulatory e-binder located within a limited access folder on the study server. We do not plan to monitor charts for AEs.

Safety information collection will begin as soon as study recruitment begins. Safety information collection will end once the participant completes the final assessment, i.e., approximately six months following completion of the intervention.

Progress Report (Quarterly)

Research staff will generate three quarterly study reports per year that outlines study progress including recruitment, retention/attrition, any protocol deviation or violation that warrants a note-to-file, and AEs, SAEs, and unanticipated problems for that particular quarter. This report will be provided to the Co-PIs and the Chair of the DSMC. The Chair of the DSMC may solicit input from the other DSMC members if she detects anything of concern (e.g., higher rates of AEs than anticipated). The Chair of the DSMC will generate a report if there is anything of concern that will be supplied to the study PIs, the UW IRB, and NCCIH.

Annual Report

Study staff will also generate an Annual Report during the last quarter of the year that will include a list and summary of any protocol deviation or violation that warrants a note-to-file, and AEs, SAEs, and unanticipated problems. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to all members of the DSMC. The DSMC along with the co-PIs will convene to review and discuss the report. The annual progress report will be forwarded to (1) the UW IRB and (2) NCCIH.

Study Report Outline for the Independent Monitors(s) (Interim or Annual Reports)

The study team will generate progress reports on a quarterly basis (three per year) for review by the Chair of the DSMC, as well as an annual report (during the final quarter of the year) to be reviewed by all DSMC members.

Study Report Outline

I. Table of Contents
II. Introduction
    a. Summary of Study Status and Issues or Problems
III. Study Administration
    a. Recruitment Status
        i. Overall Recruitment Status and Recruitment Source
        ii. Comparison of Targeted to Actual Enrollment
        iii. Reasons for Ineligibility
        iv. Reasons for Declination, Unable to Contact, Deferral
IV. Study Data Reports/Tables or Figures
    a. General Information
        i. Enrollment Status
        ii. Demographic/Baseline Data
        iii. Assessment Retention
        iv. Treatment Participation
        v. Treatment Fidelity
V. Safety Assessment
    a. SAEs
    b. Adverse Events
    c. Reportable Problems
    d. Protocol Deviations

Study Report tables will be generated only from aggregate (not by group assignment) baseline and aggregate safety data for the study population.

F5. Reporting Changes in Study Status

During the funding of this study, any action by the IRB, the DSMC, or one of the study investigators that results in a temporary or permanent suspension of the study will be reported to the NCCIH Program Officer within 1 business day of notification.

G. Potential Benefits of Research to Participants and Others

Previous studies with the therapeutic skills taught in the planned study support their efficacy in reducing pain interference and improving other pain-related outcomes. We anticipate based on this previous research that many of the participants will experience significant reductions in their daily pain interference and other benefits associated with the treatments. Participants in all three conditions will have the benefit of a caring and interested group leader, thus promoting therapeutic alliance, as well as interaction with other group members.

In our past research, many group members have expressed satisfaction from learning that there are other people with experiences similar to their own, and from receiving group treatment in a caring and nonjudgmental environment. Thus, participants in all three treatments will take away from the study new skills and knowledge regarding chronic pain and how to manage it, and – given previous results of RCTs for psychosocial interventions for chronic pain – should experience some degree of relief from pain and suffering and increases in their quality of life.

H. Publication of Research Findings

Any manuscript will be made available for review by the study sponsor prior to submission.

I. Importance of Knowledge to Be Gained

The findings from this study will provide clinically meaningful information that will have positive effects on the lives of patients with chronic pain who endorse low back pain as a primary or secondary pain problem. The findings will provide important new information regarding mechanisms of the treatments studied, as well as those factors that underlie post-treatment relapse, maintenance, and continued gains following treatment. Results will elucidate the temporal sequence of lagged mechanism effects to determine rates of change in outcome as a function of change in cognitive content, cognitive process, and behavioral activity level. Results will also precisely inform relapse prevention interventions. As pointed out by Kazdin,[12,13] progress in our understanding of treatments has been hampered by the lack of mechanism studies, such as the one planned, to identify the mechanisms of treatment outcome and relapse. The current study will help address this significant gap. The exploratory moderation findings will inform the future development of patient-treatment matching algorithms.

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Appendix: Evaluation Timeline

Assessment	Screening	Enrollment	Pre-Treatment	Baseline Monitoring Period	Treatment & Treatment Monitoring Period	Post-Treatment Monitoring Period	Post-Treatment	3-Month Follow-up	6-Month Follow-up
Inclusion/Exclusion Criteria	X								
Informed Consent		X							
Baseline Data and Demographics		X							
Pain Interference (Re-Assessment of Study Eligibility)			X						
Pain Interference (Randomization Stratification)			X						
Pain Interference (Primary Outcome)			X	X	X	X	X	X	X
Secondary Outcomes			X	X	X	X	X	X	X
Primary Mechanisms			X	X	X	X	X	X	X
Secondary Mechanisms			X	X	X	X	X	X	X
Tertiary Outcomes			X				X	X	X
Tertiary Mechanisms			X				X	X	X
Moderators			X		X		X		
Treatment Homework Completion					X				
Participant Engagement					X				
Qualitative Outcomes							X		
Optional Assessments			X				X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X