Clinical Intervention Study Protocol

Empowered Relief™

Previous Studies

Previous Study 1: "Empowered Relief" (ER) Intervention was developed by Beth Darnall, PhD at what is now the Stanford Pain Relief Innovations Lab (2014, *J Pain Res*) [7]. ER has 2 main components: education and skills acquisition. First, participants learn mind-body science as it relates to pain and PC. They learn to identify PC and how to self-treat it. Self-treatment involves applying skills to decrease physiological hyperarousal--diaphragmatic breathing and progressive muscle relaxation-- within the context of PC. Self-treatment also involves applying skills that improve cognitive and emotional regulation, including PC reframing and thought restructuring. Participants identify their typical PC thoughts and practice writing out personal reframes. Finally, self-treatment includes enacting behaviors that modulate attention and counteract helplessness. Participants self-tailor the information by developing a comprehensive plan to stop and prevent PC (See Appendix 7). Participants leave the class with the following tangibles: (1) their own written, self-crafted, personalized plan for relief; (2) a 20-minute relaxation response audio CD; and (3) a printed copy of the ER didactic content to access as needed in their PC cessation plan.

We delivered ER to 76 mixed etiology patients with chronic pain at the Stanford Pain Management Center who were referred by a treating provider. The PCS was administered at class check- in (baseline) and post-class at 2 and 4 weeks electronically. Class cohort size was 4-18 participants. The class was delivered as free clinical care and without compensation for completing two PCS follow-up measures.

Table C1. Post-Class Survey Results	0-6	
Item	**Mean**	**Percentage**
How acceptable did you find this class?	5.6	Acceptability: 94%
How satisfied are you with this class?	5.5	Satisfaction: 92%
How useful was the information presented?	5.6	Usefulness: 94%
Was the information easy to understand?	5.7	Ease of Understanding: 95%
How likely are you to use the skills and information you learned today?	5.5	Likelihood of Using Skills and Information Learned: 92%

Table C2. PCS by time point	
Time point	**Mean (SD)**
Baseline	25.47 (10.71)
Week 2	16.47 (10.52)
Week 4	13.82 (9.5)

Feasibility: We demonstrated feasibility for enrollment and successful delivery of ER across 13 class cohorts, collection of pre-post treatment data, and use of PROMIS longitudinal outcomes (Preliminary Study 2). High ratings for the 5-item post-class anonymous survey (0=very dissatisfied, 6=very satisfied) suggest that ER has good face and content validity, and that it is well-received (Table C1).

Table C3: Pain Catastrophizing Scale (PCS) Outcomes				
Clinical Significance	**Week 2**		Week 4	
	N	PCS Change From Baseline	N	PCS Change From Baseline
Increased PCS	4	+ 20.3%	0	
No Change	2	- 5.5%	3	-9.0%
Minimally Important	12	- 22.6%	5	-25.0%
Moderately Important	12	- 40.4 %	7	-38.9%
Substantially Important	13	- 61.5%	11	-72.4%

We found no differences in baseline PCS scores between those who did or did not complete follow-up questionnaires. Data included 51 participants who completed at least one follow up PCS: 67% of the full sample; Week 2, n=43 (84%); Week 4, n=34 (67%). (NB: Some participants completed only one follow-up PCS). Mean age was 49.95 (SD = 12.14) and 82% female. While patients with psychologist diagnosed depression (64%) and anxiety (70%) had higher baseline PCS scores we found no difference in absolute treatment response compared to those without the comorbidities.

Clinical Significance and Effect Sizes for ER: We used within subjects rmANOVA with time as the within-subjects factor and anxiety and depression as between subjects' factors. We found a significant linear effect for time indicating significantly reduced PCS scores at weeks 2 and 4 compared to baseline ($F = 45.97$, $p<.001$). Post-hoc paired t-tests revealed significant within subjects differences for all contrasts: PCS Baseline to PCS Week 2 ($N = 43$; $t = 6.07$, $p < 0.001$); PCS Baseline to PCS Week 4 ($N = 34$; $t = 8.36$, $p < 0.001$); and PCS Week 2 to PCS Week 4 ($N = 24$; $t = 2.51$, $p = 0.02$). Effect sizes were large for baseline to 2 and 4 week follow-up (Cohen's $d = 0.85$ and Cohen's $d = 1.15$, respectively). Importantly, these effects sizes are similar or larger than effect sizes for PC reductions reported for standard 8-session CBT-based classes [21]. While impressive, it is important to note that our study was uncontrolled and there was significant drop out inherent in the design. Accordingly, we did not use this estimate to power our study. Instead we conservatively derived anticipated effects from studies in the literature which were controlled and had various adjustments for drop-outs and missing data. Most PCS score changes in our pilot study met the IMMPACT threshold for a clinically meaningful improvement [29]. Baseline PCS did not predict treatment response—similar to other pain-CBT interventions [23]—thus suggesting that ER may be broadly appropriate for people with chronic pain. Our data suggest that treatment effects may strengthen over time with ongoing use of the personalized plan.
Relevance: ER was feasible, broadly acceptable, and significantly reduced PC at 2 and 4 weeks post-treatment. We aim to build on these promising data by conducting a rigorous comparative efficacy RCT. Preliminary data support our proposed methods to phenotype responders and non-responders.

Previous Study 2: Effect of ER on NIH PROMIS Assessments Controlling for 'Treatment as Usual'

At each visit to the Stanford Pain Management Center (SPMC) patients complete a battery of pain and psychosocial measures--including computerized automated testing (CAT) versions of the NIH PROMIS measures through the use of CHOIR (Collaborative Health Outcomes Information Registry; funded through NIH Pain Consortium HHSN 271201200728P). We examined the impact of ER across multiple PROMIS domains. 21 ER participants had CHOIR data for the following two time points: (1) 1 month pre-ER and (2) 1-3 months post-ER. (N.B. The remaining participants had no CHOIR data due to stopping treatment at the Pain Clinic. We now capture CHOIR longitudinal data from patients after clinic discharge.) Paired t-tests showed positive pre- to post-ER changes for PROMIS Pain Intensity, Pain

Interference, Depression, Sleep Disturbance, and Function ($p < 0.001$). To control for 'treatment as usual' effects we compared a clinic cohort matched to ER participants on sex, age, and PCS scores. The ER group evidenced superior improvement for PROMIS Pain Interference (Cohen's $d = 0.73$, $p < 0.001$), Pain Behavior (Cohen's $d = 0.66$, $p < 0.001$), Fatigue (Cohen's $d = 0.26$, $p = 0.05$), and Sleep Disturbance (Cohen's $d=0.46$, $p < 0.001$). Note an advantage of the NIH PROMIS is that by construction, PROMIS score effect sizes can also be estimated against the reference Census 2000 population by dividing the mean difference by 10.

Study Intervention. "**Empowered Relief (ER)":** This is a randomized control trial to examine the feasibility and preliminary efficacy of ER, which was is delivered via zoom platform. ER is a 2-hour, single-session intervention that rapidly equips people with chronic pain with pain management skills. Format of intervention: Therapist-delivered PowerPoint presentation with experiential exercises. Content of intervention: See Preliminary Study 1 (2014, *J Pain Res*).

Eligible and Interested Participants

Eligible and interested individuals will go through the Consenting Procedure. If eligible, they will be enrolled as participants and randomized after consent: Empowered Relief or Waitlist Control.

Participants will receive a survey link and complete their questions on a computer or a smartphone. Participant compliance will be monitored remotely during the baseline period, and they will also be issued reminders. During this period if participants indicate that they have developed an illness, have travel plans, or may not be able to complete baseline and treatment visits on the schedule discussed, their participation will be deferred and they will be invited to participate again after resolution of the issue(s). At the end of the deferral period (up to 3 months), their updated baseline data may be collected. To establish an accurate pre-treatment baseline for participants, the period between baseline data and start of treatment should be within one month.

Individuals not Interested or Ineligible

Individuals who are not interested or ineligible will be asked if they want their information to be included in a local database so that they may be contacted for future studies that are of interest to them.

Database Registration

The Research Staff will register all consented participant into a Central Database with their unique study ID number and demographic information.

Recruitment Contingency Plan

We have a recruitment plan in place to ensure steady enrollment. This includes recurring advertisements on Craigslist, local newspapers, direct mailers, and a presence on social media. In addition, we will plan to extract potential participants from Epic. The study recruiter will post the study flyer at OU outpatient clinics, community clinics, primary care physicians, free clinics, and other facilities to give talks on the Center for community outreach and to educate and build relationships with practitioners who can refer participants to us.

5.4 Adherence Assessment

The research coordinator will serve as fidelity rater for the ER class. In structure and format ER is optimized for treatment fidelity because it has standardized content (PowerPoint presentation; Appendix 6), and standardized handouts and materials. Only the certified CR instructor will offer the Class and the therapist's self-assessment of fidelity will be done after each ER class via REDCap Survey. We provide each instructor with the criteria that will be used to make the ratings of treatment fidelity.

5.4.1 Measures to Promote Adherence and Participant Retention

Ensuring participant understanding of study expectations:

- Knowledgeable and receptive staff: Staff education plan above ensures competent description of the study process and expectations. Staff are selected for the ability to communicate study expectations and process clearly and engage the participant in the process.
- Providing a Welcome Packet with study information and easily found contact information for study staff.

Participant Retention Measures

- Developing a personal relationship with the participant.
- Friendly staff: Staff will also be selected for their interpersonal skills and ability to engage the participant in a friendly conversation.
- Providing a thank you note to participants for participating in the study.

ER will benefit from having low attrition because it is a single-session intervention.

3. STUDY PROCEDURES

3.1 **Schedule of Evaluations** -- please see table below.

Schedule of Events

Measurement Domain/ Name of Measure	Brief Measure Description	Online Screening	Screening	Pre-treatment	Post-tx Month 0	Post-tx Months
Demographics	Age, gender, race, ethnicity, education level, household income, employment.		x			
Medical History and Medications	Height, weight, smoking, alcohol use, back pain etiology, pain duration, pain intensity, other pain conditions, pain treatments, cancer history, cancer treatment, psychological conditions, medications.			x		
Pain Catastrophizing Scale (PCS)	13-item scale assesses severity of trait pain catastrophizing tendencies on a 5-point scale (0 = "not at all"; 4 = "all the time"); sum scores range from 0-52.			x		x
Chronic Pain Self-Efficacy Scale (CPSS)	The 22 item CPSS measure will be administered to assess changes in confidence in managing pain.			x		x
Chronic Pain Acceptance Questionnaire (CPAQ-8)	Eight (8) question version CPAQ has been designed to measure acceptance of pain. The acceptance of chronic pain is thought to reduce unsuccessful attempts to avoid or control pain and thus focus on engaging in valued activities and pursuing meaningful goals.			x		x
Body Map	Interactive map of male/female body to select regions that experience pain.			x		x
Pain Bothersomeness	Single item measure of back pain bothersomeness in the past week from not at all bothersome to extremely bothersome.			x		x
Tampa scale of Kinesiophobia (TSK-13)	TSK will be administered to assess the fear related to movement causing pain			x		x
Fear of cancer recurrence (FCR)	FCR will assess the persistent worry, anxiety, and intrusive thoughts about the possibility of the cancer returning			x		x
Childhood Trauma Questionnaire	The self-report measure includes 28 items that measure 5 types of maltreatment – emotional, physical, and sexual abuse, and emotional and physical neglect. Items are measured on a 5-point Likert scale with responses ranging from never true to often true.			x		x
Patient's Global Impression of	One item measure of status change since start of treatment and one item measure of side effects.					x

Change						
Tx satisfaction, utility, and knowledge	10 items assess participant satisfaction and perceived utility of treatment on a 10-point rating scale. For the ER group, 5 items will assess knowledge acquired regarding PC and self-treatment.				x	
Treatment and Lifestyle Changes	Assesses new treatments, major lifestyle changes, major life events (negative and positive), and new injuries at different time points throughout the study.					x
Skills Use	Single item measure assessing frequency of skills use learned in class over the past month from not at all to several times per day.					x
Ambivalence over emotion expression questionnaire (AEQ)	13 items assess difficulty with expression negative emotion adaptively			x		x
Emotion Regulation Questionnaire (ERQ)	10-item questionnaire assess emotion regulation skills.			x		x
NIH PROMIS measures [54]	NIH PROMIS measures have been successfully applied in pain research [55-58] and will be used to assess multiple variables of interest, including Pain Intensity, Pain Interference, Pain Behavior, Physical Function including 4 pre-selected Mobility questions, Depression, Anxiety, Sleep Disturbance, Sleep Interference, Anger, and Fatigue. Short forms will be used to minimize participant burden. Participants also complete PROMIS Global Health at the same time point.			x		x
Pain Self-Efficacy Questionnaire (PSEQ)	10-item instrument measures self-confidence to manage pain and engage in life activities despite pain [23,26,61-64]. Pain self-efficacy be used as a mediating / moderating / process variable.			x		x

Measurement Domain/ Name of Measure	**Brief Measure Description**	**Online Screening Form**	**Baseline Period**	**Pre-treatment**	**Post-tx Month 0**	**Post-tx Months 1, 2 and 3**
Guided Relaxation (per participant discretion/goal setting; continuous data)	An app will timestamp each time an ER participant accesses the "ER Relaxation Resource" on their device, thus providing an objective measure of skills use.					X

3.2 **Description of Evaluations**

Consenting Procedure

Consent Process: Prior to collecting any in-person screening or research information, designated and trained Clinical Core staff will review the participant's IRB-approved e-Consent Form (REDCap) with him/her over the zoom, answer any questions. Each participant can download signed consent in their own device. The consenting process will be divided into two steps.

> **STEP 1 (pre-screening):** The participant will complete anonymous screening information. Once they are eligible, they will go to Step 2 of the screening to confirm their eligibility and consenting process.
>
> **STEP 2 (zoom-screening and consenting):** At this step, participants will sign the Study Consent Form and will learn in detail about the study procedures. Research staff will answer all study-related questions and make sure that the participant fully understands all procedures, tests, and visits for the study.

Storage of Consent Forms: Consent forms will be stored in the REDCap database. At the end of study, the consent will be printed and stored in a binder labeled "PHI and Consent Forms for ER RCT" and dated. The binder(s) will be stored in locked cabinets. Each consent form will be labeled in the upper right corner with subject ID number.

Eligibility

Inclusion: Age – 18 or older, history of cancer diagnosis, completion of active cancer treatment, cancer free at the time of enrollment, experience of body pain most or every day, pain duration at least 3 months, English fluency

Exclusion: significant psychological and cognitive impairment that limits one's ability to complete study tasks (completion of online survey, attending the zoom-based ER class). Life-threatening acute illness (e.g., infection, heart attack, injury), and no access to a computer, a smartphone or a tablet.

Participants not interested or ineligible

Participants who are not interested or ineligible will be asked if they want their information to be included in the lab Central Database so that they may be contacted for future studies that are of interest to them.

6.2.1 Enrollment, Baseline, and/or Randomization

Enrollment

If all eligibility criteria are met as stated above, the participant will undergo Step 2 of the Consenting Procedure and mentioned above in the Consenting Procedure section. This is the point of enrollment of the participant into the study. The enrollment date will be recorded in the lab Central Database. The enrollment date will also be recorded on the Screening and Enrollment CRF, which will have a schedule of future visits.

Empowered Relief: ER will be delivered via a PowerPoint presentation to groups of participants in a single-session lasting approximately two hours. The single-session may be delivered online.

Content: ER has two main components: didactics and skills acquisition. Didactic content includes mind–

body science as it relates to pain and PC. Participants learn how to identify unhelpful thought patterns in the moment, and how to self-treat it. During the class, participants acquire skills and develop a plan to apply the learned skills to decrease physiological hyperarousal – diaphragmatic breathing and progressive muscle relaxation – within the context of unhelpful thought patterns (pain catastrophizing). Participants also acquire skills that improve the regulation of cognition and emotion, including thought reframing and thought restructuring, and develop a plan for implementing these skills in daily life. During the class participants identify their typical unhelpful thoughts and practice writing out their reframes. Finally, participants develop a plan to use behaviors that modulate attention and counteract helplessness. During the class, participants create personalized lists of self- soothing behaviors; lists are customized to various settings. Participants self-tailor the information relayed during the class by developing their own comprehensive self-treatment plan to stop and prevent catastrophizing. Participants leave the class with the following tangibles: 1) their self- written, self-crafted plan for pain relief; 2) a 20-minute relaxation response audio file; and 3) a printed copy of the Empowered Relief slides to access as needed.

Online Follow-Up: Participants will complete online assessments at weeks 4, 8, and 12. The study staff will also make phone calls to remind participants to complete the online follow-up questionnaires.

6.2.2 Assessments

6.2.3 Study Completion

- **Project Stop Point CRF:** Research staff will complete second half of project stop point CRF after participant completes their last online follow-up. At this point, it will be indicated on the CRF that all follow-up visits are complete and the participant's record will be closed.

Note: All post-treatment surveys must be completed within 2 weeks following each post-treatment time point. We have multiple systems in place to ensure data is collected within days of survey deployment. Our survey system will close and locked 2 weeks following survey.

4. SAFETY ASSESSMENTS

There are no adverse events anticipated.

4.1 Specification of Safety Parameters

Not applicable

4.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Not applicable

4.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign, syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recording regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

There are no SAEs anticipated for this research study.

Selection Criteria

These selection criteria derive from our analysis of the tradeoff between using highly restrictive inclusion criteria in order to have a "pure" sample and using few inclusion criteria to increase generalizability of results to the community. Participants must meet all of the following inclusion criteria in order to be enrolled in the study:

- Pain duration ≥ 3 months
- English fluency
- Age – 18 or older
- History of cancer diagnosis,
- Completion of active cancer treatment
- Cancer free at the time of enrollment
- Experience of body pain most or every day
- Pain duration at least 3 months

All candidates meeting any of the exclusion criteria below at screening will be excluded from the study.

- Gross cognitive impairment
- Participating in any psychology interventions that improve pain self-management skills and pain coping (Cognitive Behavioral Therapy, Acceptance and Commitment Therapy, Mindfulness, etc.)
- Clear likelihood to disrupt fellow class participants (e.g., personality disorder) at the discretion of the study team
- Significant psychological impairment (e.g., severe depression) that limits one's ability to complete study tasks (completion of online survey, attending the zoom-based ER class).
- Life-threatening acute illness (e.g., infection, heart attack, injury)
- No access to a computer, a smartphone or a tablet.

4.4 **Definition of Populations**

ITT (Intent to treat) refers to all participants who have completed the screening visit and have been randomized to 1 of 3 arms.

Per protocol refers to participants who have completed treatment and the post-treatment assessment.

4.5 **Interim Analyses and Stopping Rules**

The treatments in this study are not associated with risks.

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

We do not anticipate any adverse effects from this intervention.

4.6 **Outcomes**

Our design is a randomized 2-arm study with test treatment and waitlist control arms. Our goals are to provide scientific evidence to demonstrate the efficacy of ER, and also provide a comparison of said efficacy against the waitlist control. Treatment allocation is randomized to minimize confounder effects. Statisticians performing analyses will be blinded.

9.5.1 Primary Outcome

Aim 1: Feasibility of "Empowered Relief" (ER)

For Aim 1, We hypothesized that ER would (a) be feasible (as indexed by 75% attendance rate, an average treatment satisfaction rating of ≥ 8 on a 0-10 scale, and successful recruitment of 250 within three-year period)

Hypothesis 1: ER will be feasibility in cancer survivors with chronic pain

Aim 2: Preliminary Efficacy of ER

Primary endpoint: Primary outcomes (pain intensity, pain interference, pain bothersomeness) at 3-month post treatment.

Hypothesis 2a. ER will be significantly better in reducing these outcomes at 3-month post-treatment compared to the Waitlist control.

Hypothesis 2b (Reducing depression, anxiety, anger, social isolation, and quality of life) ER will be significantly better in reducing the psychosocial symptoms at 3-month post-treatment compared to the waitlist control.

Hypothesis 2c (Improving pain coping variables – pain catastrophizing, pain self-efficacy, pain acceptance, fear of movement, emotion regulation): ER will be significantly better in improving pain-related coping at 1-month post treatment compared to the waitlist control and this improvement will be maintained at 3-month post-treatment.

Primary 1 Analyses: rmANOVA will be used.

Aim 3 (Qualitative Data): Zoom-interview will be conducted to deeply understand the ER experience and to receive feedback on how to improve the ER class for cancer survivors.

9.6 Data Analyses

Specific analyses to be conducted are detailed in Section 9.5 above. We will examine whether there are any between-group differences in the above mentioned variables using a single multivariate GLM. If there are any between-group differences, we will include the variable(s) as covariates in our subsequent analyses.

Subject Adherence and Intention to Treat (ITT) and Per Protocol (PP) Analyses: A portion of subjects will be lost to follow-up. Attrition assumption is typically 25% in the pain-CBT literature [24]. We conservatively estimate a 20% attrition for ER. Thus, our study completion target of 100 subjects in each arm indicates a need to (over)enroll a total of 125 subjects for both the ER and WL control groups**.** Data analysis will be performed primarily as intention-to-treat (ITT) to protect the effects of randomization from confounding introduced by subject dropout and crossover. Compared to PP analysis, ITT is also considered conservative in hypothesis testing (Hypotheses 2, which are used to

power this study). With regards to missing data, we will attempt to follow all participants, even if they withdraw from allocated treatment. A main analysis will be performed of all valid observed data under a plausible assumption about the missing data. This will be followed by sensitivity analyses that accounts for all randomized patients, to explore the effect of departures from the assumption made in the main analysis.

5. DATA COLLECTION AND QUALITY ASSURANCE

5.1 Data Collection Forms

All questionnaires will be completed by participants in the REDCap Database. If some questionnaires have to be collected on paper due to unforeseen circumstances, the forms will be stored as source data and a member of the study team will enter the data into the REDCap database. A note indicating this occurrence will be made and added to the participant record.

All participants will be identified by a unique study ID number on their corresponding data and case report forms and will not be identified by their name. All CRFs will be stored in REDCap or in binders identified by the Participant ID number and stored in locked cabinets by the study staff Core. All staff will receive training on completing CRFs appropriately, reviewing CRFs for completeness, and maintaining participant confidentiality.

5.2 Data Management

All collected data will be managed by the study staff. As mentioned above, all data will be de-identified and stored in locked cabinets to ensure participant confidentiality. All data collection forms filled out by the participant will be administered via REDCap.

5.3 Quality Assurance

10.3.1 Training

All research team members will perform the responsibilities as outlined by the delegation of authority log. Human Subjects Training and HIPAA training will occur as required by Stanford Policy. Additionally, all team members will receive a copy of this document, the Lab Policy Manual, and will be trained directly by the Principal Investigator (PI) on the purpose of the study and their responsibilities. Research staff will be trained on Informed Consent, Zoom Screening, and Case Report Form Completion by the study coordinator, who will monitor appropriate conduct and form completion on an ongoing basis, in collaboration with the Division Research Manager and the PIs. Research team meetings will occur frequently with the PI to ensure ongoing understanding by study staff and to address any concerns.

<u>Regulatory and Ethical Training Requirements</u>

The study coordinator will ensure that all study personnel have completed required federal and institutional training, and will maintain documentation of such. The coordinator will assist with the scheduling of training workshops, development of training agendas, and preparation of materials to reinforce ethical research and Good Clinical Practices.

- Human Subjects Protections: Training will include guidelines related to: HIPAA regulations and participant confidentiality, ethical research conduct, and human subjects interactions.
- Conflict of Interest: Compliance with Stanford's conflict of interest policies and ongoing monitoring will also be provided.

10.3.2 Quality Control Committee

The study personnel will conduct internal monitoring of case report form completion and protocol adherence on a quarterly basis.

10.3.3 Metrics

The metric for the primary outcome measure is self-reported pain intensity, pain interference, and pain bothersomeness.

10.3.4 Protocol Deviations

A major protocol deviation or violation includes any procedure that differs from the IRB approved protocol that was intended to eliminate an immediate hazard to the participant, was harmful, or is possible serious or continue non-compliance by a study staff member.

Major protocol deviations will be communicated by the research staff to the PIs immediately. All events will be communicated to NCCIH within 5 days of the PI learning of the event. A description of the event will be included. The research staff will also submit this information to the IRB.

All minor protocol deviations (those that do not meet the definition of a major deviation and do not affect the interpretation or outcome of the study) will be reported to NCCIH and Stanford IRB annually.

For each participant, a Protocol Deviations Log will be maintained with the participant's record. A comprehensive Protocol Deviations Log will be maintained by the research staff.

10.3.5 Monitoring

Trial Monitoring

Adverse Events, Serious Adverse Events, Unanticipated Problems, and Protocol Deviations will be monitored on a continual basis and reported per information in the relevant sections.

A trained research assistant will monitor participant attendance and adherence, as well as class instructor treatment fidelity.

Additional ongoing monitoring will occur as detailed below. Results will be recorded on the Monitoring CRF. The PI will review and sign-off on the results and any suggested resolutions.

The first 10 participants will have case report forms and consent forms reviewed for accuracy and completion immediately after enrollment and entry into the follow-up period. After the first 10 participants, case report forms and consent forms will be evaluated for completeness every 3 months.

The study team will be responsible for monitoring the study and compiling a report of the results, which will be sent to the entire study team and results will be discussed study team meetings. Ongoing issues with data completion will be addressed with the individual team member and re-training may occur as necessary.

Case Report Form Completion

Data discrepancies will be compared to any source data and corrections made by crossing out the original value, providing the correct value, dating, initialing, and providing a reason for the correction (corrections can be made this way in REDCap). Missing data or data discrepancies that cannot be resolved by verifying source data will be left as missing.

Consent Form Completion

Consent forms will be evaluated for completeness of all signatures, required initials, and dates. Any missing signatures will be obtained by mailing the participant a copy of the consent form and requesting the signature with the current date. Any missing study staff signatures will be obtained and dated with the current date. Participants with missing signatures who are unable, or unwilling, to provide missing signature will be withdrawn from the study and data will not be used.

6. PARTICIPANT RIGHTS AND CONFIDENTIALITY

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

6.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the Stanford IRB and NCCIH.

6.2 Informed Consent Forms

A signed consent form will be obtained from each participant. Participants must be able to understand all the study procedures in order to be successfully consented. Therefore, only English-speakers will be consented for the study. Individuals under the age of 18 will not be included in the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A signed copy will be given to each participant and this fact will be documented in the participant's record.

6.3 Participant Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NCCIH, and the OHRP.

6.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

7. Optional treatment for participants in the waitlist control.

7.1 Optional Secondary Study: There will be an optional secondary study embedded within the clinical trial to provide additional support for the study hypotheses.

7.2 Optional ER Treatment for the Waitlist Control Group: Upon completion of all study procedures at the 3-month post-treatment assessment, participants in the waitlist control group will be offered an optional ER class. If a sufficient number of participants (n ≥ 30) complete the ER class and associated outcome measures, the following hypotheses will be tested.

Hypothesis 3a. Participation in ER will result in significant reductions in pain intensity, pain interference, and pain bothersomeness from pre- to post-ER.

Hypothesis 3b. Participation in ER will result in significant reductions in depressive symptoms, anxiety, anger, and social isolation from pre- to post-ER.

Hypothesis 3c. Participation in ER will result in significant improvements in pain-related coping variables (pain catastrophizing, pain self-efficacy, pain acceptance, fear of movement, and emotion regulation) from pre-treatment to 1-month post-treatment, with improvements maintained at 3-month post-treatment.

Analytic Approach (Hypothesis 3).
Within-group changes over time will be examined using repeated-measures ANOVA (rmANOVA).

8. COMMITTEES

The key personnel of this study will serve as a committee to review and make decisions concerning this study.

9. PUBLICATION OF RESEARCH FINDINGS

Any publication will be made available for review by the key personnel of this study prior to submission.

10. REFERENCES

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11. SUPPLEMENTS/APPENDICES

Appendix 1 – Schedule of Events and Compensation at each task

RCT						
	Pre-screening	Zoom-screen & Consent	Randomization & Baseline	ER class	Post-ER survey	Follow-up 1, 2, and 3 months
ER	x	x	x	x	x	x
Compensation	None	None	$20	None	$25	$25, 30, & 35
WL	x	x	x		x	x
Compensation	None	None	$20	None	None	$25, 30, & 35

Optional for WL group after completing RCT 3-month follow-up					
	ER class	Post-ER survey	Follow-up 1, 2, and 3 months		
ER	x	x	x		
Compensation	None	$25	$25, 30, & 35		

A small group for a zoom interview (N = 20) $30

Appendix 2 – Participant timeline

Randomized to

1. **Intervention**: Baseline survey → ER class → post-class survey → Surveys at 1, 2, and 3 months after ER
2. **Waitlist**: Baseline Survey → Surveys at 1, 2, and 3 months → *optional ER class → post-class survey → Surveys at 1, 2, and 3 months after ER

* Optional ER will be offered to all participants in Waitlist.

**The first 20 participants will be interviewed for qualitative data collection via Zoom-interview