PARTNERS HUMAN RESEARCH COMMITTEE DETAILED PROTOCOL

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Protocol Title: Toolkit for Optimal Recovery after Orthopedic Injury; A multi-site feasibility study to prevent persistent pain and disability

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I. BACKGROUND AND SIGNIFICANCE

Acute orthopedic musculoskeletal injuries are prevalent and costly.

Acute musculoskeletal orthopedic injuries (e.g., fractures, dislocations, also known as traumatic musculoskeletal injuries) represent the leading cause of adult hospital admissions[1]. Approximately 20-50% of patients go on to develop persistent (e.g., chronic) pain and disability[1,15] despite making adequate recovery of their bones and soft tissues. These patients tend continue to have multiple surgeries and medical appointments, resulting in increased health care costs and a significant public health burden[2,3].

Psychosocial factors in the acute phase after the orthopedic injury, predict chronic pain and disability.

Catastrophic thinking about pain, pain anxiety, depression, and prolonged opioid use are established risk factors for disability and pain in patients with musculoskeletal injuries[4–10], regardless of the severity[10,15,16], location[8,17] or type of injury[6,18,19]. Recognizing these psychosocial factors early in the recovery process creates a window of opportunity to identify and intervene with patients who are at risk for chronic pain and disability in the acute phase, when psychosocial treatments are most effective[20,21]. A recent systematic review conducted by our team showed that there are no evidence based psychosocial treatments targeting psychosocial factors in patients with acute orthopedic injuries[22]. This provides urgency for the development of feasible, accepted, evidence-based interventions to prevent chronic pain and disability in at risk patients with orthopedic musculoskeletal injuries early in the recovery process, along with medical care.

The care of patients with orthopedic musculoskeletal injuries follows an outdated biomedical model.

Current usual care for patients with acute traumatic musculoskeletal injuries consists primarily of surgical interventions and pain medications. However, medical care is undergoing a shift in priorities recognizing the multifactorial influences on successful recovery after injury, and the pivotal role of psychosocial factors within orthopedic care[23, 24]. Although surgeons are now aware of the importance of psychosocial factors in recovery after musculoskeletal injuries[12], they are often uncomfortable referring patients for outpatient care[12,25,26]. Referrals are often done after multiple unsuccessful medical procedures, when patients have become invested in a medical cure, pain has already become chronic, and treatments are generally less efficacious[25,26].

Further, engaging pain patients in traditional mental health treatments has been challenging due to stigma associated with mental health concerns among this population[7,23]. Referrals are also challenging due to lack of trained providers, particularly for patients in rural areas for whom travel to clinic for additional visits would be an additional burden. Travel to clinic is a burden even for patients who are geographically proximal to clinic but are often unable to drive and have to rely on family and friends for transportation.

Mind body approaches delivered to patients with acute orthopedic injuries may help.

Over the last decade, mind-body interventions have demonstrated utility for improving psychological and pain-related outcomes and have potential to help patients who seek care for musculoskeletal injuries in orthopedic surgical practices as an adjunct to medical care[27–36]. Brief mind body programs show promise among orthopedic patients[37]. In a fully powered randomized controlled single blinded study we have shown that a 60-seconds, personalized, live video mindfulness exercise is highly accepted, feasible and useful for patients with non-traumatic hand and upper extremity orthopedic conditions waiting for their medical appointment with a surgeon, and is associated with momentary decrease in pain and distress compared to an attention placebo control[38].

We developed the first mind-body program – The Toolkit for Optimal Recovery after orthopedic injury (TOR) – to prevent chronic pain and disability in at-risk patients with orthopedic injuries. We used the fear avoidance model as the theoretical framework to guide the development of TOR.[51] The fear avoidance model provides a useful framework to understand the transition from acute to persistent or chronic symptoms in patients with acute orthopedic injuries. The model specifies that catastrophic thinking about pain (i.e., misattributions about pain), and anxiety about pain (i.e., hypervigilance to pain sensations) lead to avoidance of activity and escape behaviors, which in turn, lead to increased pain and disability. Using this model and feedback from surgeons and patients with acute orthopedic injuries, we iteratively developed a 4-session, individual, live video mind-body program, TOR, focused on optimizing recovery and preventing chronic pain and disability in patients with orthopedic injuries who endorse catastrophic thinking about pain and/or pain anxiety and are thus at risk for chronic pain and disability, based on our prior work.

TOR directly targets catastrophic thinking about pain (i.e., misconceptions about pain and activity, hopelessness, helplessness and magnification of pain) and pain anxiety (i.e., cognitive, physiological and pain avoidance elements) through teaching relaxation response and mindfulness skills, correction of misconceptions (e.g., through education and adaptive thinking techniques), acceptance and value-based engagement in activities, and activity pacing. The goal is to "confront" rather than "avoid" the pain experienced and activities that may be associated with pain and thus prevent the transition toward chronic pain. Each TOR session is about 45 minutes, and all 4 are delivered within a period of 4-5 weeks (TOR and control arm will be yoked for the timing of interventions). Brief mind-body interventions have shown to be feasible to implement and acceptable to patients in busy orthopedic practices. The live video delivery format aims to bypass established barriers to biopsychosocial care for orthopedic patients (e.g., transportation, inflexible schedules)[30]. These format/dosage considerations are all in line with feedback we received from surgeons and patients with acute orthopedic injuries during the iterative treatment development process. It is unlikely that TOR intervention causes any risk of physical or psychological harm other than potential experience of psychological discomfort while discussing their experiences during intervention sessions. As indicated, our pilot feasibility RCT of TOR at MGH showed evidence for feasibility, acceptability, and satisfaction for TOR.

II. SPECIFIC AIMS

Aim 1 (Year 1): Develop a semi-structured qualitative interview script that will be used to conduct separate focus groups with surgeons and with supportive medical staff (e.g., nurses, medical assistants) at the 3 original sites.

Deliverables: 1) Develop a study protocol including milestones, and strategies to maximize success of Aim 2; 2) develop education materials to facilitate referrals and study procedures for surgeons and staff; and 3) finalize the Toolkit for Optimal Recovery after Orthopedic (TOR), as needed; 4) anticipate and develop alternative plans for potential study challenges, at each site.

Aim 2 (Years 2, 3, & 4): Conduct a 4-site feasibility RCT (180 participants total, 60 at the parent site, 50 completers; 40 per child site; 33-34 completers per site) to compare the TOR versus a minimally enhanced usual care control (MEUC). The trial will be informed by our preliminary data and activities of Aim 1. This trial will be used to 1) determine whether the study methodology and TOR meet a priori set benchmarks necessary for the success of a subsequent efficacy trial and 2) determine whether the study methodology and TOR meet a priori set benchmarks for the 27 secondary outcomes related to the success of the subsequent efficacy trial. After the conclusion of the intervention, we will also solicit feedback from orthopedic trauma providers about their perceptions of the feasibility, acceptability, and appropriateness of the TOR study in their clinic.

Deliverables: 1) refined protocol of patient recruitment, study protocol, and fidelity materials, 2) study procedures that are individualized to each site and feasible, appropriate, and accepted by patients and staff, and have the potential to decrease pain and increase physical function/decrease disability; 3) ability to meet feasibility, acceptability, appropriateness and fidelity benchmarks at each of the 4 sites in preparation for the UG3/UH3.

The PI has experience adapting and conducting mind body interventions via videoconferencing, and has received IRB approval on 2 ongoing studies assessing efficacy of mind body interventions via videoconferencing that are currently progressing.

III. SUBJECT SELECTION

All adult, English-speaking, 18 or older patients presenting to the each of the 3 Level 1 Trauma Centers sites with a traumatic musculoskeletal injury will be invited to enroll. The study will be described in detail and a member of the IRB-approved study staff trained in obtaining consent will obtain informed consent. Patients will be given a copy of the consent form and be informed that their participation is voluntary and that they can withdraw at any time. Subjects will be identified by referrals through surgeons and other orthopedic medical providers. We will aim at

recruiting N = 60 participants at the parent site and N = 40 participants per child site (total N = 180).

Aim 1: Inclusion/Exclusion Criteria

Eligible participants must meet the following inclusion criteria:

1) Male and female medical staff (surgeon, fellow, resident, nurse, medical assistant, front desk, phone, research staff) in the Level 1 Trauma Center of one of the 3 sites.
2) Willingness to participate

One or more of the following exclusion criteria will render a participant ineligible:

1) Chief of orthopedic trauma

Aim 2: Inclusion/Exclusion Criteria

Eligible patients must meet the following inclusion criteria:

1) Outpatient adults in the Level 1 Trauma Center at the 4 sites
2) Age 18 or older
3) Able to meaningfully participate (English fluency and literacy, stable living situation as determined by the medical staff at each site).
4) A score of 8/10 or more on the Short Portable Mental Status Questionnaire ONLY IF a participant is 65 or older, or if a participant's cognitive abilities are unclear to research staff
5) Sustained one or more acute orthopedic injuries (e.g., fracture, dislocation, rupture) approximately 1-2 months earlier (acute phase).
6) PCS $\geq$20 or PASS-20 $\geq$40
7) Willingness to comply with the study protocol, including randomization, questionnaire completion, and potential home practice and weekly sessions.
8) No psychotropics for at least 2 weeks prior to initiation of treatment or stable for >6 weeks and willing to maintain a stable dose
9) Cleared by orthopedic surgeon for activities using the injured limb within the next 4 weeks

One or more of the following exclusion criteria will render a patient ineligible:

1) Serious comorbidity expected to worsen in the next 6 months (e.g., malignancy)
2) Current untreated or unstable severe mental health conditions like bipolar disorder, schizophrenia, or active substance use
3) Current suicidal ideation
4) Other unmanaged serious non-orthopedic injuries that occurred alongside the orthopedic injury (i.e., TBI, ruptured internal organs, etc.)
5) Currently in litigation or under Workman's Comp
6) Surgery complications (e.g., uncontrolled infection, need for repeat surgery)
7) Self-reported pregnancy
8) Practice of meditation, or other mind body techniques that elicit the RR, for at least 45 total min a week each week over the last 3 months

After the conclusion of the RCT, we will also solicit feedback from orthopedic trauma providers (up to 80 participants total) about their perceptions of the feasibility, acceptability, and appropriateness of the TOR study in their clinic.

Eligible participants must meet the following inclusion criteria:

1) Male and female medical staff (surgeon, fellow, resident, nurse, medical assistant, front desk, phone, research staff) in the Level 1 Trauma Center of one of the 4 sites.
2) Willingness to participate

Recruitment

Aim 1: Participants will be surgeons and medical staff at each of the 4 sites. We will conduct separate focus groups with surgeons and with the rest of the medical staff. Trauma chiefs (Co-Is on this grant) will not be included in the focus groups to avoid bias. The site PI and surgeon champion at each site, with support from the trauma chiefs will give presentations during the staff meetings to discuss the aim of the study, present preliminary data, discuss potential benefits to patients, and encourage participation. The RA at each site will next assist with recruitment, consent, and scheduling focus groups.

Aim 2: Participants will be recruited from each of the 4 Level 1 Trauma Center sites: MGH, Kentucky, Dell and Vanderbilt following a recruitment protocol developed and individualized for each site, consistent with prior recommendations[13,14], and informed by aim 1. Potential participants will be identified through screening of the medical record by the RA (injury in the prior 1-2 months, consistent with our preliminary data). The RA will next notify the medical staff (medical assistant) who will alert the surgeons. The surgeon will do a "warm hand-off" and introduce the RA and the study to the participants at the end of the medical visit. The RA will assess for eligibility (per criteria above). All participants will sign a consent form in REDCap prior to study procedures. All forms of recruitment will be submitted for IBR approval prior to use. Participants who meet eligibility criteria will complete baseline questionnaires on an iPad or on paper in clinic. The RA will be available to answer any questions.

Eligible cases may also be identified by daily screening of Epic admission reports.

After the conclusion of the intervention, we will also solicit feedback from orthopedic trauma providers about their perceptions of the feasibility, acceptability, and appropriateness of the TOR study in their clinic. Participants will be surgeons and medical staff at each of the 4 sites. Site PIs and surgeon champions will distribute survey links via email to providers at their site. After reviewing a consent fact sheet, participants will be asked to complete a brief demographic questionnaire as well as a brief survey regarding their perceptions on the implementation of the TOR study in their clinic (11 items).

IV. SUBJECT ENROLLMENT

Aim 1: Surgeons and medical staff at the original 3 sites will be asked to participate in focus groups. It is anticipated that focus groups will comprise the following participants: 4 surgeon attendings, 1 fellow, 2 residents, 2 medical assistants, 1 nurse, 2 front desk staff, and 4

administrative assistants (MGH); 5 surgeons attendings, 27 fellows, 8 medical assistants, 2 nurses, 4 front desk staff (Kentucky); 4 attendings, 8 fellows, 2 nurses, 4 medical assistant, 6 front desk staff, and 10 other stuff (e.g., schedulers, orthopedic technicians) (Dell). We have the full support from the orthopedic leadership at each site for these activities.

For Aim 1, we will obtain verbal consent from the medical professionals who agree to participate in the focus group sessions. Prior to verbal consent, study staff will inform participants that the focus group discussions will be audio recorded, as these recordings will be utilized to inform implementation of our mind-body intervention. All participants will be ensured that participation is strictly voluntary and confidential, and that it does not affect their care at any of the Partners Healthcare institutions. In addition, we will inform the participants about the confidentiality measures that the research group will take during the process. Only members of the research team will have access to the data, and the recorded transcriptions will be de-identified as to not contain identifiable or confidential information. The verbal consent process will include pertinent information on study design, risks and benefits, and voluntary nature of the research and confidentiality. Due to the nature of this study and the minimum risk, we would like to waive the written documentation of informed consent. However, study staff will document verbal consent by retaining a list of names of the participants who verbally consented and participated in the focus group. The consent process will be executed in a manner consistent with the IRB approved protocol, and the most recent version of the IRB-approved protocol will be used. Participants will be encouraged to review the study fact sheet, in its entirety, before verbally consenting. Study staff will answer any questions that participants may have. Participants will be given a copy of the fact sheet.

Aim 2: Participants will be recruited from each of the 4 Level 1 Trauma Center sites: MGH, Kentucky, Dell and Vanderbilt following a recruitment protocol developed and individualized for each site, consistent with prior recommendations[13,14], and informed by aim 1. Participants will be patients with acute orthopedic musculoskeletal injuries who are at risk for chronic pain and disability (PCS $\geq$ 20 and PASS-20 $\geq$ 40) and meet inclusionary/exclusionary criteria. Informed by guidelines for feasibility testing[69] and Proctor's framework[13]. Potential participants will be identified through screening of the medical record by the RA (injury/surgery in the prior 1-2 months, consistent with our preliminary data). Study staff will ask all participants to provide verbal consent to participate in screening procedures prior to screening. This will happen in clinic when the participant arrives or over the phone prior to the clinic visit. The verbal consent will be documented. The RA will further assess for eligibility and conduct initial screening (using the PASS and PCS) and will notify the orthopedic surgeon that the patient is a potential study participant (verbally or via a note with the study logo attached to the door). Surgeons will also receive information regarding race and ethnicity of each participant in order to prioritize study referrals. The orthopedic surgeon will perform the medical visit and subsequently introduce the study to the potential participant using a predetermined script and materials/procedures. For the patients who express interest or want to learn more, the surgeon will conduct a "warm hand off" referral to the research assistant. The research assistant will finish the screening process using the screening checklist. If there are challenges in recruitment due to time required for study procedures, participants will be screened by study staff via phone prior to coming in for their 1–2-month follow-up visit so that they can be notified in advance if they are eligible to budget time for the research visit.

If a participant meets all study criteria, the RA will meet with the participant in a private location following their clinic visit to describe the study in detail including the consent form. All patients will have the opportunity to ask questions and will be given time to consider whether or not to participate. Participants will be informed of the potential risks and benefits of participation, and information regarding who they can contact for further questions. They will also be informed that participation is voluntary, that they can refuse to answer any questions, and they can withdraw from the study at any time. They will be informed that refusal to participate in the study will in no way impact their medical care. All participants will sign a consent form electronically in REDCap prior to study procedures. Participants will sign on an iPad in the clinic, or participants will be given the option to sign the consent form at home prior to completing study procedures remotely**.** Consent will include provision of consent to receive once daily text reminders to complete home practice (if randomized to TOR) as well as once daily reminders to record skills practiced (if randomized to TOR). All forms of recruitment will be submitted for IRB approval prior to use. Participants who meet eligibility criteria and consent will complete baseline questionnaires on an iPad or on paper in a private location in the clinic. The RA will be available to answer any questions. A trained research assistant will assist with the grip test (for upper extremity injuries) or walk test (for lower extremity injuries). Next, they will be randomized to TOR or Minimally Enhanced Usual Care (MEUC) and will receive a patient manual (TOR) or booklet (MEUC). Participants in both TOR and MEUC will also be provided with access to a website that contains the information from the treatment manual (for TOR) or printed booklet (for MEUC) and be assisted in accessing this website from their preferred device and bookmarking the website (e.g., downloading as an app), as desired. For those randomized to TOR the RA will install the Zoom secure live video platform on the participants' smart phones. For those who prefer to use a laptop, desktop or iPad, the RA will email a link and schedule a call to assist with the set up. The RA will also download the study website with pre-recorded TOR skills onto the participants' phones in an app form to aid with skills consolidation/practice. If enrolled participants do not have reliable access to a smartphone or other device or internet, the RA will provide the participant with a smartphone and set up a short-term data plan to enable participation in the study. Finally, the RA will schedule the first individual virtual visit with the clinician.

For the provider feedback surveys, surgeons and medical staff at each of the 4 sites will be asked to participate. Up to 80 providers are expected to participate. Medical professionals who choose to participate will provide implied consent based on their review of a study fact sheet in REDCap. All potential participants will be provided with a study fact sheet as the first page of a REDCap survey. The study fact sheet provides detailed information on the methodology and purpose of the study and the potential benefits/ risks associated with participating. All participants will be ensured that participation is strictly voluntary and confidential. In addition, the study fact sheet will inform the participants about the confidentiality measures that the research group will take during the process. Only members of the research team will have access to the data, and data will be de-identified as to not contain identifiable or confidential information. The study fact sheet will include pertinent information on study design, risks and benefits, and voluntary nature of the research and confidentiality. Participants will be encouraged to review the study fact sheet in its entirety before continuing to complete the brief REDCap survey. The study fact sheet will also contain the names and numbers of members of study staff that participants can contact if they have additional questions

or concerns. Due to the nature of this study and the minimum risk, we would like to waive the written documentation of informed consent. The consent process will be executed in a manner consistent with the IRB approved protocol, and the most recent version of the IRB-approved protocol will be used.

V. STUDY PROCEDURES

Aim 1: Participants will be surgeons and medical staff at the original 3 sites. Participants will provide verbal informed consent prior to participation. Participants will be informed their participation in voluntary and they are not obligated to answer any questions. Next, we will conduct separate focus groups with surgeons and with the rest of the medical staff. Trauma chiefs (Co-Is on this grant) will not be included in the focus groups to avoid bias. The site PI and surgeon champion at each site, with support from the trauma chiefs will give presentations during the staff meetings to discuss the aim of the study, present preliminary data, discuss potential benefits to patients, and encourage participation. The RA at each site will next assist with recruitment, consent, and scheduling focus groups. For MGH surgeons, ideal focus groups are at 6:30 am or 7:00 am. Each site will prioritize recruitment, and the number of focus groups will depend on ability to schedule participants at each site. Exit interviews will be administered immediately after.

Aim 2: We will conduct a 4-site feasibility RCT and recruit 180 participants total (60 at the parent site, 50 completers; 40 per child site**,** 33-34 completers).

Baseline and follow-up assessments will include measurements of grip strength (for upper extremity injuries) or a walking test (for lower extremity injuries), which measures the time required to travel 10 meters, self-report measures assessing the primary (pain intensity and disability), and secondary (depression, PTSD, pain catastrophizing and pain anxiety) variables, and demographic information. Patients will complete the following reliable and valid battery of questionnaires, which will take approximately 20 minutes to complete:

- Demographics: Age, gender, race/ethnicity, education, employment, income, marital status, current psychotropic/pain medication intake, comorbid medical conditions, history of depression or other mental health conditions.
- Clinical variables: Injury type, date, location, prior pain (all by self report).
- Pain: Numerical Rating Scale, requires the patient to rate their pain on a defined scale (11-point scale from 0 (no pain) to 10 (worst pain)).
- Pain: Use of analgesics; Concomitant treatment: Daily self-report log.
- Physical function self-report: PROMIS Physical Function assesses one's ability to carry out activities that require physical actions, ranging from self-care to social and work.
- Physical function self-report: Short Musculoskeletal Function Assessment assesses patient’s function as well as how bothered they are by their injury.
- Emotional function: The Center for Epidemiologic Study of Depression measures self-reported symptoms of depression.

- Emotional function: The PTSD Checklist civilian version measures symptoms of PTS.
- Coping: Pain Catastrophizing Scale assesses hopelessness, helplessness and rumination about pain.
- Coping: Pain Anxiety Scale, short form assesses avoidance, fearful thinking, cognitive and somatic symptoms of anxiety.
- Coping: Measures of Current Status (MOCS) assesses ability to engage in a series of healthy coping skills (e.g., relaxation, social support, adaptive thinking).
- Credibility and Expectancy Scale
- Mindfulness: 15-item Five-Facet Mindfulness Questionnaire (FFMQ-15)
- Experiential Avoidance: Acceptance and Action Questionnaire (AAQ-2)

Subjects will complete these questionnaires in the clinic or if there is not enough time, a researcher will send the questionnaires via a secure REDCap link for participants to complete at their home. At the 4 week follow up (after the intervention), they will also complete the Client Satisfaction Questionnaire[49] to assess satisfaction with intervention. Patients will complete these measures on line via REDCap either in the clinic or from home. The walk test will be performed near a wall and a researcher will accompany the subject for the duration of the test. The subject will be informed that they should use the wall or researcher for balance, if needed, and this will be recorded. The grip strength test is routinely performed by researchers as part of other research projects in the department. The protocol for training and safety to ensure the reliability of results will be followed for this study. The grip strength test and walk test will be optional and subjects can refuse participation. Subjects may experience minimal pain during these exercises. The researchers will check the subject's medical record for any potential restrictions in activity and discuss with the treating physician any concerns about safety. We expect that most of the healing would have already occurred because we will be enrolling subjects about 0-3 months post injury date. Subjects in wheelchairs will not participate in the walk test.

Next, following guidelines for psychosocial clinical trials[43], we plan for a 1:1 RCT comparing 2 arms: 1) TOR (delivered via Zoom) + MEUC and 2) MEUC. Patients will be randomized based on scores on Pain Catastrophizing (PCS) and Pain Anxiety (PASS). PCS and PASS were chosen for the randomization based on our prior work with this population, which showed that PCS was the strongest predictor of pain intensity and PASS of long term disability[2]. This method of randomization (median split on PASS and PCS) was successful in our previous face to face RCT[1]. We will stratify participants by site, using the randomization module in REDCap, which will be prepared using permuted blocks by the study statistician. Out of the 180 participants enrolled, 90 will be randomized to TOR and 90 to MEUC. Within the 60 participants at the parent site, 30 will be randomized to TOR and 30 to MEUC. Within each of the 40 participants at the child sites, 20 will be randomized to TOR and 20 to MEUC. We will report on our primary and secondary outcomes specifically for each site (separate by study site strata). There will be 3 assessment points for the intervention: 1) baseline (0-3 months post trauma and before the intervention), 2) first follow-up post intervention (4 weeks post baseline), 3) second follow-up post intervention (3 months post baseline).

TOR has been developed tested and found efficacious in improving disability, pain, mood and coping in patients with orthopedic trauma, and we are ready to test it via videoconferencing to improve access to care. TOR has 4 sessions, 45 minutes each. TOR is focused on 1) discussing

the rationale for treatment and conducting motivational interviewing, 2) cognitive restructuring of patients' negative thoughts/misconceptions, 3) teaching patients to elicit the relaxation response through breathing retraining, progressive muscle relaxation and guided imagery, 4) helping patient decrease avoidance and return to activities including the injured limb, 5) increasing resiliency and preventing relapse. In both groups, patients will receive usual medical care (e.g., pain medications, physical therapy, and meetings with surgeons, medical staff) as currently delivered by orthopedic surgeons. In addition, participants in the control group, will receive a booklet containing brief summarized information that reflects the active intervention topics including the trajectory of pain and recovery after orthopedic illness, the role of relaxation strategies to manage pain and the importance of returning to engagement in activities of daily living. Participants in the MEUC will also be provided with access to a website that contains the educational information from the printed booklet in electronic format and be assisted in accessing this website from their preferred device and bookmarking the website, as desired. Participants in MEUC who do not own a smart phone will not be provided with one as they can also access the educational information in printed form access to a website that contains the educational information from the printed booklet in electronic format. The randomization process will increase likelihood of comparability of the two groups on the main study variable pain catastrophizing. Clinical staff at MGH will deliver TOR to participants at all sites.

Participants randomized to TOR will undergo set-up for the live video intervention prior to leaving the clinic. This includes: 1) installing Zoom and teaching participants how to use it; 2) scheduling their 4 weekly intervention sessions with the clinician; 3) setting up EZ texting to receive reminders; and 4) installing the TOR web platform (with session content and guided exercises) as an app on their phones. Participants who do not own a smart phone will be given one, and the RA will set their phone up at the first visit. We will also provide study participants with a data plan for the duration of the study, or brainstorm ways to access free internet (e.g., library, friends' houses), if needed. Our study team has used these strategies in prior studies. The RA will also schedule the participant's first session of TOR and ensure the participant writes down the date and time of the first session.

In order to ensure that participants in the TOR program are familiar with Zoom, the psychologist will schedule a brief session to go over how the software works and prepare the participants for the intervention.

Participants randomized to TOR will also receive daily text reminders through Twilio to practice program skills as well as record their skills practice if they consent to receive text reminders.

For the provider feedback surveys, surgeons and medical staff at each of the 4 sites will be asked to participate. Up to 80 providers are expected to participate. Participants will provide implied informed consent prior to participation. After reviewing a consent fact sheet, participants will be asked to complete a brief demographic questionnaire as well as a brief survey regarding their perceptions on the implementation of the TOR study in their clinic (11 items). Site PIs and surgeon champions will distribute surveys to providers at their site. We have the full support from the orthopedic leadership at each site for these activities.

VI. BIOSTATISTIC ANALYSIS

Aim 1:

We will use qualitative interviews and exit interviews to identify further understand the patient flow and clinic structure at each site, assess surgeon and staff perceptions and barriers and facilitators for study implementation and referrals, provide description of the TOR skills and perception of the utility of the TOR components (including suggestions for potential modifications), understand surgeon and medical staff beliefs and attitudes toward biopsychosocial care at each site, and learn barriers and facilitators for making patient referrals. The qualitative focus group data and individual exit interview data will be transcribed and analyzed, using NVivo 10 qualitative software, and we will conduct thematic content analysis using guidelines provided by Miles and Huberman[67]. The 2 coders (study clinicians) will meet on an ongoing basis with Dr. Vranceanu and Elwy to discuss the structural thematic framework, categories, and coding plan, guided by the Proctor Framework, but allowing for the emergence of additional codes[68]. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. Coding will continue until a high reliability (Kappa= >0.80) is established. Once these data analyses are completed, the multidisciplinary team will provide the expert review of data, to discuss the interpretation of our findings in the context of current research on chronic heterogeneous pain. We will also work on identifying whether site specific themes emerged that would require tailoring the training materials as well as staff training and methodology for aim 2 to each site.

Aim 2:

The main purpose of this multi-site feasibility RCT is to assess feasibility, acceptability, appropriateness and fidelity of TOR and study procedures at each of the 4 sites, to meet benchmarks before an efficacy trial. We will calculate, for each site, number of patients identified via medical record, number referred by surgeon, number screened, number consented, number enrolled and randomized. The results will be reported using descriptive statistics (numbers, proportions, and mean scores).

Given the feasibility RCT design, the trial is not fully powered for efficacy. Consistent with the feasibility design of this trial, we will report means and SDs of all measures at all time points, including distribution of scores and internal consistency. To determine the measures' sensitivity to detect change, we will report within group change in all quantitative outcomes. We will also conduct exploratory between group analyses to inform the future fully powered RCT.

VII. RISKS AND DISCOMFORTS

Aim 2:

The greatest discomfort associated with participation is the time required to complete the questionnaires and grip strength and walk test measurements. Subjects might experience minimal pain when completing these tests. Study physicians will be readily available should a subject experience discomfort while completing the measurements. The grip strength and walk test are

optional and subjects can refuse participation. Questionnaires and measurements will require approximately 25 minutes at the time of enrollment and about 25 minutes at the 3-month follow-up.

Patients are not obligated to answer any question. The patient's participation will not affect their medical care. Patients can withdraw from the study at any time. Patients who are disturbed by any of the questions will be offered psychological counseling, referral to a psychiatrist, or immediate transfer to the emergency room for psychiatric evaluation, depending upon the severity of the reaction.

Study physicians will be readily accessible for consultation should a study patient experience increasing discomfort while completing the questionnaire or during the intervention time period. In the extremely unlikely event that a patient has a severe adverse emotional disturbance while completing the questionnaire, we will contact the Acute Psychiatric Service and immediately take the patient to the Emergency Department for treatment. Subjects removed to the Emergency Department for additional care will not be asked to complete the questionnaires and will be dropped from the study.

VIII. POTENTIAL BENEFITS

Aim 1: No direct benefit is anticipated.

Aim 2: No direct benefit is anticipated. Participants may improve their ability to cope with pain and improve their mood, pain, and disability. Information gained through this study may lead to a better understanding the importance of delivery method of mind body interventions.

IX. MONITORING AND QUALITY ASSURANCE

Electronic information will be stored in REDCap (Research Electronic Data Capture), a free, secure, and HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing Enterprise Research Infrastructure & Services (ERIS) group (based at the PHS Needham corporate datacenter). Data will be stored on password protected computers that will be stored in secure locations at all times. Paper data files (with coded subject identification) will be stored in a locked filing cabinet. Only research staff will have access to these data locations.

A unique anonymous identifier will be assigned to each subject; subsequently, all data collected will be associated exclusively with this identifier. This includes all questionnaires administered over the course of the study, as well as home practice logs.

Data from this study will be stored for three years after the publication of all study results, at which time all paper data files will be shredded, and computer files will be deleted.

The following study staff will be blinded: 1) overall PI; 2) site PIs; 3) surgeon champions; 4) study statistician; 5) RA involved with any post and follow up self-report and objective assessments; 6) statistician who is performing blinded analyses.

To achieve RA blindness, treatment assignment will done by randomization RA, who will not be directly involved in evaluation or data collection. Survey data collection will be conducted by another RA who will be blinded to participant treatment assignment. Participant self-report surveys will be implemented using secured online survey software, which will significantly limit the potential of the RA to introduce bias. The overall PI, site PIs and surgeon champions will not be involved in the group assignment or collection of data. Also analyses will be conducted when data are unlocked. The study statistician and statistician who perform blinding analysis will not have access to randomization algorithm key.

The following study staff will not be blinded: 1) randomization RA (RA who will randomize participants after consent and baseline and give participants study materials consistent with their respective treatment arm, and problem solves in real time and potential tech issues for those in TOR); 2) study therapists/clinicians; 3) the statistician who will develop the randomization scheme. The unblinded staff will have no access to data and no involvement in data monitoring and analyses.

Data Management and Quality Control Procedures

To maximize accuracy and security, all survey data will be collected and stored on REDCap. Research staff will ensure that proper consent has been obtained before sending the REDCap survey to each participant.

REDCap (Research Electronic Data Capture) is a free, secure, HIPAA compliant web-based application hosted by the Partners HealthCare Research Computing Enterprise Research Infrastructure & Services (ERIS) group. Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, has developed this software toolset and workflow methodology for electronic collection and management of research and clinical study data. Data collection projects rely on a study-specific data dictionary defined by members of the research team with planning assistance from Harvard Catalyst, The Harvard Clinical and Translational Science Center EDC Support Staff. This iterative development and testing process results in a well-planned data collection strategy for individual studies. Using REDCap, the research team can also design web-based surveys and engage potential respondents using a variety of notification methods. REDCap provides flexible features that can be used for a variety of research projects and provides an intuitive interface to enter data with real time validation (automated data type and range checks). The system offers easy data manipulation with audit trails, reports for monitoring and querying participant records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

Since consistency of application of the study protocol is critical to acquiring high quality data, all research personnel have undergone or will undergo a competency-based training program prior to enrolling subjects.

Data and Safety Monitoring Plan

Study data will be maintained in a locked filing cabinet and on password protected computers. Questionnaires and self-reported responses will not become part of the patient's medical record

and will not contain medical record numbers or names. Hardcopies of study related data and forms will be stored in a lockable file cabinet. Patient information will remain confidential by keeping identifying information (name, medical record number, and subject number) in a separate locked file cabinet. Only the investigators and study staff specified on the consent form will have access to this information

Among the 4 recruitment sites (MGH, Dell, Kentucky, Vanderbilt), PHI will be shared related to enrolled study participants. MGH will send and receive PHI to/from Dell, Kentucky and Vanderbilt using encrypted email as well as shared storage in the Partners-approved platform Dropbox. PHI will not be shared with any study collaborators outside of MGH, Dell, Kentucky and Vanderbilt. Once data collection is completed, all data will be de-identified. Our collaborator at Brown University will receive only de-identified data.

The study research assistant will be trained in procedures to protect study participant confidentiality. All data will be kept confidential, stored on password protected drives accessed through encrypted devices, accessible only to trained study staff. Participants' data will be identified by ID number only, and a link between names and ID numbers will be stored separately and securely. Session recordings will be immediately downloaded from the recording device to the secure computer and subsequently deleted from the recording device. Recordings will be labeled with the patient ID and stored on a password protected computer; the recording will be subsequently and immediately deleted from the recording device. Just like a regular doctor's appointment, the live-video visit will be kept private and confidential. The research team will report to the data safety and monitoring committee with details of any participant confidentiality breach and corresponding plans for corrective action. Data for all participants will be kept strictly confidential, except as mandated by law or as necessary for monitoring by IRB, or NCCIH. In the unlikely event of serious concerns of suicidality and to ensure patient safety, we will suspend confidentiality and alert the site PIs so that appropriate clinical interventions can be assured.

All study staff have been trained in responsible research conduct through a CITI course. The RAs will be trained on the importance of maintaining confidentiality through the assignment of ID numbers. All data will be kept confidential, on password protected drives accessed through encrypted devices only, accessible only to trained study staff. Participant data will be identified by ID number only, and a link between names and ID numbers will be saved separately. Session recordings will be immediately downloaded from the recording device to the secure computer and subsequently deleted from the recording device. Recordings will be labeled with the patient ID and password protected.

Adverse Event Monitoring: Throughout the study subjects will be monitored for the occurrence of events defined as any undesirable experience or unanticipated risk. Lack of effect of treatment is not considered an event. All adverse events will be reported on an adverse event form. The Principle Investigator has the responsibility of reporting serious adverse events (death, life threatening illness or injury, serious injury, or permanent disability) to PHRC within 24-72 hours of notification.

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