Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

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For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

mTBIs are prevalent and costly.

Mild Traumatic Brain Injuries (mTBIs), also known as concussions, are common and costly. In the United States, there are almost 3 million emergency room visits for TBI each year – a 47% increase over the past decade – resulting in a cost exceeding $60 billion. [1] mTBIs account for the vast majority of TBIs, with an estimated incidence of up to 600/100,000 per year. Nearly all patients report physical (e.g., headache), emotional (e.g., irritability), behavioral (e.g., insomnia) and cognitive (e.g., difficulty concentrating) symptoms in the week after an mTBI.[2] Although many patients make a full recovery after mTBI, a substantial portion experience persistent (e.g., chronic) symptoms that can become intractable over time. Indeed, at 3-months post injury, up to 64%[3] of patients with mTBI continue to report three or more persistent symptoms, followed by little to no improvement thereafter. Thus, it is critical to provide early interventions to prevent symptom persistence.

Psychosocial factors after TBI predict symptoms persistence and disability.

Symptom persistence after mTBI reflects a complex mind-body interaction. Unlike moderate-to-severe TBI, the prognosis of mTBI is not well correlated with injury severity or clinical findings.[4] Rather, a large body of research shows that persistent symptoms after mTBI are a prototypical application of the biopsychosocial model, in which psychosocial factors contribute to the development and maintenance of symptoms and disability. In particular, anxiety, which is particularly common among patients with mTBI, has emerged as an important modifiable risk factor for poor prognosis. Up to 70% of patients with mTBI report anxiety symptoms, and 21-36% meet diagnostic criteria for an anxiety disorder.[5,6] Studies testing multivariable models to predict symptom persistence among individuals with mTBI have reliably showed that anxiety is one of the strongest predictors of symptom persistence and functional impairment.[4,7]

Anxiety may contribute to symptom persistence after mTBI by mimicking or amplifying symptoms, increasing hypervigilance and misattributions, and motivating activity avoidance. First, anxiety causes many of the physical, emotional, cognitive, and behavioral symptoms that also occur after mTBI. Thus, it is possible that patients with anxiety misattribute symptoms common to both conditions (e.g., difficulty concentrating, irritability, insomnia) to the mTBI, when in fact the symptoms are likely due to ongoing anxiety.[8] Second, patients with anxiety are

hypervigilant towards perceived threats, including physical symptoms, misattribute them (e.g. catastrophize them), which contributes to increased symptom reporting.[9] Third, avoidance behaviors, which are characteristic responses to anxiety, may contribute to symptom persistence and disability. For example, long-term rest in healthy individuals has been shown to induce non-specific symptoms common to mTBI, including headache and fatigue.[10,11] Activity avoidance also interferes with occupational, social, and recreational functioning, thus contributing to disability and reduced quality of life.[12] These mechanisms are consistent with the fear-avoidance theoretical model which explains transition from acute to chronic pain, [13] and provide a useful conceptualization for how anxiety causes or amplifies mTBI symptoms, and leads to symptom persistence. My work has examined and found support for the fear avoidance model among patients with mTBI. Specifically, this work showed that both catastrophizing and activity avoidance mediate the relationship between anxiety and post-concussion symptoms among patients with mTBI. [14]

Unlike moderate and severe TBI, current guidelines for mTBI management have moved away from the "wait and see" and "rest until symptom free" approaches. [11] Rather, experts now agree that re-engagement in activities of daily living is healthy and promotes recovery, while inactivity induces or maintains non-specific symptoms and perpetuates activity avoidance. [11] For patients with anxiety, following these recommendations is challenging due to maladaptive beliefs that activity should be avoided, and physiological manifestations that mimic post-concussion symptoms. As such, patients with anxiety and mTBI are at risk for decreased functioning across occupational, social, and recreational contexts and persistent symptoms. To date, there are no evidence-based interventions for patients with acute mTBI and comorbid anxiety focused on breaking the cycle of avoidance and preventing symptom persistence. It is thus critical to develop a prevention intervention that is feasible, accepted and efficacious.

Mind body approaches delivered to patients with mTBI may help.
Mind-body interventions effectively treat both individual symptoms common to mTBI (e.g., insomnia, [15] headache[16], and fatigue[16]) and anxiety.[17] Further, they have also been shown to reduce stigma associated with traditional mental health referrals[18] and are already popular among patients with neurological concerns. [19]
Mind-body interventions can be effectively delivered via live video.[20,21] Live video represents a promising avenue for delivering preventative care for individuals with acute mTBI and anxiety, who face many barriers to in-person visits such as symptom burden, the time and cost associated with travel, the decreased flexibility in scheduling, the lower access to trained providers relative to live video delivery. [22] Our team has extensive experience with the development and delivery of pilot and fully powered randomized controlled trials of mind-body interventions delivered via live video. [23,24] Most relevant to this proposal, our team has developed a brief live video mind-body treatment, the Toolkit for Optimal Recovery After Injury (TOR) [25] to prevent chronic pain after acute injuries in those with high anxiety and catastrophic thinking about pain. We plan to adapt this program for the specific needs of patients with acute mTBI and anxiety, who are at risk for persistent post concussive symptoms (Toolkit for Optimal Recovery after Concussion; TOR-C).
Young adults are an optimal target for this proposal for 4 main reasons. First, sports-related injuries, a main cause of mTBI, [26,27] are particularly common among individuals aged 24 or younger. [28,29,30] Second, the rates of anxiety are also high (~ 40%) among this age-group, even in

the absence of an injury. [31] Third, this population is particularly vulnerable to adverse effects on functioning following prolonged mTBI symptoms due to the demands of young adulthood as well as the neural plasticity and ongoing brain development associated with this age.[32] Fourth, college-age individuals prefer live video conferencing over in-person interventions. [33] Finally, our team has access to this specific population of mTBI patients.

2. Specific Aims and Objectives

Aim: Conduct a randomized controlled trial (N=Up to 55) of the TOR-C versus a control health education program (HEP). We will use this information to determine if the TOR-C is effective in preventing chronic pain and improving anxiety in college-age individuals with acute mTBI and comorbid anxiety compared to the control program.

Deliverables: 1) Refined protocol of patient recruitment, study protocol, and fidelity materials, and 2) ability to meet feasibility, acceptability, appropriateness and fidelity benchmarks in preparation for a future efficacy randomized controlled trial (RCT).

3. General Description of Study Design

Design and methodology are informed by the Obesity Related Behavioral Intervention Trials (ORBIT) and National Center for Complementary and Integrative Health (NCCIH) models of intervention development, which emphasize the importance of iteratively optimizing interventions to establish feasibility markers before efficacy testing.

4. Subject Selection

We will aim to maximize the inclusion of racial and ethnic minorities within the study. The MGH Sports Concussion Clinic draws patients from a wide geographical region, including urban Boston, surrounding communities, and the entire New England area. The recruited sample from MGH will resemble the patient population at MGH (2016 statistics) in its ethnic composition (70% white, 12% Hispanic; 10% black; 6% Asian, 14% native Hawaiian/pacific islander, American Indian/Alaska-Native, or others). We developed strategies to ensure recruitment of racial and ethnic minority samples using recommendations from Ibrahim & Sidani, 2014. Such strategies include: 1) training study staff in culturally sensitive communication and recruitment strategies focused on being flexible, and building rapport; 2) providing educational information to clinicians at the MGH Sports Concussion Clinic about the pivotal role of diverse opinions from diverse individuals; 3) prioritizing approaching every racial and ethnic minority patient presenting to the MGH Sports Concussion Clinic. Our team has successfully increased the recruitment of minority patients in our MGH studies using this methodology. The goal will be to ensure that patients of the all racial and ethnic backgrounds feel that they are part of a community that aims to improve quality of care for concussion patients.

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Diagnosed with mTBI with onset 3-10 weeks earlier (confirmed by clinic staff)
2. Clinically significant anxiety symptoms (score ≥ 5 on GAD-7 anxiety scale)[34]
3. Age 18-35

4. English fluency and literacy
5. Ability and willingness to answer questionnaires and participate in a 4-session intervention
6. Cleared for participation by clinic/study staff

Exclusion Criteria

1. Participation in mind-body or CBT treatment in the past 3 months
2. Concussion in the past 2 years that resulted in symptoms lasting 3 months or more / current or previous complicated or moderate/severe TBI
3. Practice of mindfulness techniques > 45 minutes/week in the past 3 months
4. Psychotropic medications (e.g. antidepressant, anxiolytics) changed in the past 6 weeks
5. Psychosis, uncontrolled bipolar disorder, active substance dependence, self-reported current active suicidal ideation with plan and/or intent.
6. Pregnancy
7. Secondary gains that may bias motivation (e.g., pending disability claim)
8. Serious comorbidity expected to worsen in the next 6 months

Participants will be individuals between the ages of 18 and 35 recruited from MGH Sports Concussion Clinic, MGH Emergency Department, in addition to concussion clinics nationwide, college health resources (e.g., sports medicine centers, campus disability access offices, student health services), relevant public social media sites (e.g., Facebook groups), Research Invitations via Patient Gateway after identifying potential participants through Research Patient Database Registry (RPDR) queries, and Partners Rally. Screening and informed consent will take place either in person or remotely. Participants who receive the flyer will have the option to scan a QR code and provide their contact information for remote screening.

5. Subject Enrollment

The screening and consent process will occur in-person or remotely. During the restrictions of the COVID-19 pandemic, all recruitment procedures will be performed remotely (e.g. interactions with concussion clinic staff, screening over the phone, electronically sending the consent form, etc.) For remote screening and consent, participants will be emailed a consent form through RedCap, and screening will be conducted by the research assistant over the phone. For in-person screening and consent (whenever allowed according to MGH and CDC guidelines), the screening will be conducted face-to-face, and participants will be handed a hard copy of the consent form. The screening form includes a statement about the preference for correspondence over secure vs. unencrypted email, details about the risks using unencrypted email, and a place for the participant to state their preference.

After screening and review of the consent form, if participants choose to continue with the study, study staff will collect contact information, for the RA to assist participants with Zoom live-video software installation as needed, and schedule a time for the first program session. Participants will set up a time to download Zoom and learn how to use the platform if needed and will schedule their 4 sessions.

6. Study Procedures

Participants will be individuals between the ages of 18 and 35 recruited from MGH Sports Concussion Clinic, MGH Emergency Department, in addition to concussion clinics nationwide, college health resources (e.g., sports medicine centers, campus disability access offices, student health services), relevant public social media sites (e.g., Facebook groups), Research Invitations via Patient Gateway after identifying potential participants through Research Patient Database Registry (RPDR) queries, and Partners Rally. Screening and informed consent will take place either in person or remotely. During the restrictions of the COVID-19 pandemic, all recruitment procedures will be performed remotely (e.g. interactions with concussion clinic staff, screening over the phone, electronically sending the study fact sheet, etc.). Remote screening calls and general study information may be disseminated over email prior to enrollment for the convenience of the potential participant and RA. All participants who provide their email over REDCap prior to screening will be informed of the security risks associated with email communication using standard MGB language. Additionally, if it is their preference, participants will have the option to communicate via unencrypted email with the understanding that MGB will not be held responsible for any data breaches. For remote screening and consent, participants will be emailed the study consent form through RedCap, and screening will be conducted by the research assistant over the phone. For in-person screening and consent (whenever allowed according to MGH and CDC guidelines), the screening will be conducted face-to-face, and participants will be handed a hard copy of the consent form. The screening form includes a statement about the preference for correspondence over secure vs. unencrypted email, details about the risks using unencrypted email, and a place for the participant to state their preference.

After consenting, participants will set up a time to download Zoom and learn how to use the platform if needed and will schedule their 4 sessions. After scheduling, participants will be sent a secure REDCap link to complete baseline questionnaires at their home or another private location and will be asked to complete these before their first session. Following completion of the baseline survey, participants will be randomized to either the experimental intervention or health education control condition. There will be 2 assessment points following the baseline: post-test (4 weeks later, upon completion of the program) and 3-month follow-up (3 months following post-test).
The Toolkit for Optimal Recovery after concussion (TOR-C) program, adapted during Aim 2 of the study, focuses on addressing mind-body skills that elicit the relaxation response (e.g., body scan, deep breathing, mindfulness), cognitive-behavioral strategies (e.g., reframing), acceptance and commitment skills (e.g., acceptances), and skills for returning to activity (e.g., goal setting, activity pacing). Participants randomly assigned to this intervention condition will receive daily text reminders to practice program skills as well as record their skills practice via methods such as Twilio if they consent to receive text reminders. A health education program will serve as the control condition for this aim of the study and will teach participants about health topics such as sleep, nutrition, and exercise. Participants randomly assigned to this control condition will not be assigned homework and will not receive daily text reminders. All participants (regardless of randomization) that consent to text messages, may receive text reminders for sessions and/or assessments (disseminated through EZ Texting).

The following measures will be administered at all timepoints unless otherwise stated:

Demographics (baseline only)

Credibility and Expectancy Questionnaire (baseline only)
Post-Concussion Symptom Scale
General Anxiety Disorder (GAD-7)
Hospital Anxiety and Depression Scale (HADS)
WHO Disability Assessment Scale (WHODAS) 2.0 (12-item version validated for mTBI)
Fear Avoidance Behavior after Traumatic Brain Injury (FAB-TBI)
Pain Catastrophizing Scale (PCS)
Cognitive and Affective Mindfulness Scale (CAMS-R)
Behavioral Response to Illness (BRIQ; limiting behavior and all or nothing behavior subscales)
Client Satisfaction Questionnaire (post-test only)
Medication Change (post-test only)

Participants will be compensated $20 for the baseline assessment, $30 for the post-test assessment, and $40 for the 3-month follow up assessment, for a total of $90 for participation in the study. Participants will be made aware of this in the study flyer, during the screening process and in the consent form.

7. Risks and Discomforts

There is no risk of physical injury to participants. Participants with active suicidality will not be enrolled. However, in the case that any potential participant endorses active suicidality while screening, the trained research assistant will immediately contact Principle Investigator or study clinician, who will do a risk assessment. If needed, the participant will be referred to a higher level of care, including going to the nearest emergency room. A similar procedure will be followed if active suicidal ideation is raised during the intervention or at any other point of contact with the participant. Safety will always be prioritized over study participation.

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. The PI and study clinician will be readily accessible for consultation should a study patient experience increasing discomfort while completing the questionnaire. In the extremely unlikely event that a patient has a severe adverse emotional disturbance while completing screening, the trained research assistant will immediately contact Principal Investigator or study clinician, while the participant is on the line to conduct a thorough risk assessment. If needed, the participant will be referred to a higher level of care, including going to the nearest emergency room. A similar procedure will be followed if active suicidal ideation is raised during the interview or at any other point of contact with the participant. Safety will always be prioritized over study participation.

Collecting identifiable information carries the risk of loss of confidentiality. However, we will take numerous steps to minimize this risk. Study data will be maintained in a locked filing cabinet and on password protected computers on Partners encrypted SFAs. Interviews 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. Prior to the audio-recorded interview, participants will be instated not to share identifiable information, and if they do, it will be omitted by study staff in the transcription process.

8. Benefits

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. All participants in this study will be offered the information from the 4-session Toolkit for Optimal Recovery after Concussion program, if they aren't randomized to that condition.

9. Statistical Analysis

Frequency and proportions will be used to assess feasibility of recruitment and retention procedures. Proportions of patients with scores over the midpoint on the Client Satisfaction Questionnaire and the Credibility and Expectancy Questionnaire will be used to assess satisfaction and credibility of both conditions.

10. Monitoring and Quality Assurance

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.

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). All data will be stored on password protected computers that will be stored in secure locations at all times. Only research staff will have access to these data locations.

Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept on a separate folder on a Partners SFA. Recordings will be immediately deleted from the digital recording device and stored under password protection.

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

The PI will monitor the validity of the data and adherence to the IRB approved protocol on a daily basis. A member of study staff will verify that all items on all questionnaires have been addressed. Data will be checked for out of range values using frequency distributions prior to analyzing the data. The PI will be responsible for ensuring compliance with IRB procedures.

11. Select the Privacy and Confidentiality measures that apply to this research:

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

Describe below:

12. References

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