Adapted Cognitive Behavioral Treatment for Depression in Patients with Moderate to Severe Traumatic Brain Injury

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DETAILED PROTOCOL v. 18.0
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I. BACKGROUND SIGNIFICANCE

TBI: Scope of the Problem: Approximately 1.7 million traumatic brain injury (TBI) related emergency department visits, hospitalizations, and deaths occur each year in the US.[1] Further, both military and civilian medical centers are confronted with an influx of TBI cases due to military involvement in Iraq and Afghanistan.[2] Following TBI, individuals face physical, cognitive, emotional, and behavioral consequences that impair overall functioning, such as dependence upon others, inability to work, and problems with interpersonal relationships. About 1.1% of the US population is living with long-term disability as a result of TBI[3] and one of every five individuals hospitalized due to a TBI does not return to work one year later.[4] Estimates of the cost of TBI are substantial, ranging from $60.4 billion[4] to $221 billion annually,[5] accounting for medical costs, productivity loss, and lost quality of life. Patients with moderate to severe TBI endure average healthcare costs 5.75 times greater than matched controls.[6] In addition, roughly 40% of TBI patients suffer from two or more psychiatric disorders,[7] and the cost of care is 3.4 times greater for patients with moderate to severe TBI and psychiatric illness than patients with TBI and no psychiatric illness.[6]

Depression after TBI: Major Depressive Disorder (MDD) is the most common psychiatric illness in patients with TBI,[8] often impeding the recovery process and resulting in long-term impairment in functioning.[9] The prevalence of depression in TBI has ranged from 6% to 77% using clinical rating scales[10] and from 17% to 61% using diagnostic criteria.[11] Although the risk for developing MDD is significant in the first year after TBI (53.1% of patients hospitalized for TBI),[12] increased risk for depression persists many years after the injury.[13] Depressive symptoms are associated with worse global outcomes in the first six months,[14] and up to five to seven years after the injury.[15] Individuals with MDD following TBI experience greater problems with attention, memory, processing speed, and executive functioning than patients with TBI and no depression.[16,17] Further, MDD following TBI is associated with higher prevalence of aggression[18] and suicidal behaviors.[19,20,21]

The mechanisms of post-TBI depression are not well understood. It is reasonable to hypothesize that some processes driving the onset and maintenance of post-TBI depression may be specific to TBI, while some may be shared with individuals without TBI.[9] TBI may cause changes in brain function that initiate the development of symptoms that mimic the clinical presentation of MDD in the acute or subacute post-TBI phase.[22] Some evidence suggests that neuronal and glial loss in the prefrontal and hippocampal regions of the brain may contribute to post-TBI depression.[23,24] Genetic, developmental, and psychosocial factors may also contribute to the development of post-TBI depression.[25] Psychological vulnerability, awareness of disability, activity or physical limitations, and social disruption following TBI may contribute to the maintenance or delayed onset of chronic psychiatric symptoms.[24] Some studies have suggested that psychologic and environmental factors may be more critical in the development of post-TBI depression than changes in brain function caused by the TBI.[26,27] One model of post-

TBI depression suggests that negative self-appraisal and self-appraisal of disability are strongly correlated with depression, and that depression is significantly related to functional outcome independent of injury severity and disability.[27] Taken together, current evidence supports a biopsychosocial model of post-TBI depression that is likely to have significant treatment implications.

Treatment of Depression in TBI: Similar to our understanding of the mechanisms of post-TBI depression, there is limited understanding about the efficacy of treatment. Further, there are no evidence-based guidelines for the treatment of MDD in patients with TBI. Standard treatments for depression in patients with TBI and mood symptoms, such as pharmacological treatments,[11,28,29,30,31] cognitive behavioral therapy (CBT),[32,33,34,35] physical exercise,[36,37,38,39,40] and multidisciplinary, psychosocial interventions[41,42] have been examined and present mixed findings.[43] Moreover, most studies did not require subjects to meet criteria for MDD and were not designed to prospectively treat MDD. The majority of these studies did not have the methodological rigor (i.e., randomized controlled trials, large samples, clear entry criteria) necessary to draw definitive conclusions on the efficacy of traditional treatment for MDD in patients with TBI, and clinicians are forced to rely on clinical judgment and recommendations used for other populations.[44] Relying on guidelines developed for the general population is problematic given that patients with TBI and psychiatric problems may not respond as well as patients without TBI to traditional psychotherapeutic interventions as a result of TBI-specific impairments (i.e., impaired cognition).[45] A recent meta-analysis of treatments for depression following *mild TBI* revealed that active treatment is no more beneficial than placebo,[46] suggesting that standard depression treatment may not be enough and needs to be adapted to address other issues following TBI.

Given the strong association between self-appraisal of post-TBI ability and depression[27] and the effectiveness of CBT for depression in the general population,[47,48] CBT may be an ideal intervention to adapt for individuals with MDD and TBI. As such, studies on CBT for depressive symptoms in TBI have been encouraging. However, effects were modest, often indicating only partial symptom reduction and large variability.[11,43] Moreover, none of the four studies that included cognitive behavioral interventions for depression in TBI and demonstrated some improvements in depressive symptoms[32,33,34,35] were designed specifically to treat individuals with MDD. This is problematic because the efficacy of CBT for MDD following TBI cannot be concluded from studies of individuals with subthreshold symptoms, given that comparatively greater illness severity, impairment in functioning, number of recurrent episodes, and risk of relapse are often evident in individuals with MDD.[49] Further, the intervention tested by Bradbury et al.[34] was education-matched (not randomized controlled), designed to treat "emotional distress," and included individuals with TBI as well as non-traumatic brain injuries (i.e., due to stroke, tumor, fall). Topolevec-Vranic et al.[32] executed a study of internet-delivered CBT that was not controlled and Tiersky et al.[33] examined a comprehensive treatment program that presents significant challenges to feasibility (i.e., cost, resources) and implementation. Finally, Bédard et al.[35] did not find consistent reductions in depressive symptoms across measures, resulting in inconclusive results about the superiority of mindfulness based cognitive therapy over wait-list control for individuals with depressive symptoms following TBI. Taken together, small samples, imprecise study criteria, and heterogeneous selection of assessment measures and study design limit the ability to make comparisons across studies and draw definitive conclusions about the efficacy of CBT interventions in this population.

Nonetheless, CBT has significant promise in the treatment of MDD following TBI when it is effectively adapted to address the needs of individuals with TBI. Two recent studies of TBI-tailored CBT were prospectively designed to target depression. Fann et al.[50] examined telephone and in-person CBT for DSM-IV[51] diagnosed MDD tailored for individuals with TBI. Although preliminary findings suggest that minimally adapted CBT may be more helpful in treating MDD than a control group after 8 weeks, the study had 1) inconsistent findings across primary and secondary measures, 2) a study design that included choice stratification and a biased usual care group, and 3) small, heterogenous sample (18 subjects completed in-person CBT). After 16 weeks, the outcomes for the CBT group were similar to the usual care group. Ashman et al. [52] compared the efficacy of TBI-tailored CBT and supportive psychotherapy in a sample of 77 individuals with depression and mild to severe TBI and found no differences in outcomes between interventions. Of note, the study was comprised of a heterogeneous sample in terms of 1) TBI severity and 2) duration of time since injury (average > 10 years), and it demonstrated overall low response to treatment. Relatively long duration of time since injury may suggest a sample of participants with treatment resistant depression who are likely to be qualitatively different from individuals who have experienced less time since TBI. In addition, the study utilized a very active comparison group and found no significant moderating variables, thus providing no clear explanation about the lack of significant findings. Given the paucity of research and outstanding questions about the efficacy of an adapted CBT for MDD in individuals with TBI, further research is needed.[50,52]

Adapting Cognitive Behavioral Treatment will Improve Outcomes: Despite the promise of CBT in treating MDD in patients with TBI, there are a number of difficulties that distinguish depressed individuals with TBI from depressed individuals without TBI.[16] Thus, there have been strong recommendations to modify psychological interventions to address the specific needs of individuals with TBI.[53] Individuals with TBI typically experience significant neuropsychiatric sequelae, which can impede the rehabilitation process.[54,55] Some of the most persistent cognitive problems after TBI include difficulties with attention, concentration and memory.[56] Attention impairments among those with TBI are multifaceted but can include lowered vigilance, increased distractibility, slowed processing time, and impaired ability to attend to various aspects of one's environment.[57] Many individuals also experience deficits in executive functioning skills, such as problem solving, working memory, abstract reasoning, planning, conceptual flexibility, and organization.[55,58] In addition, patients with moderate to severe TBIs often experience deficits in social cognition (e.g., emotion perception, cognitive empathy)[59] which can interfere with interpersonal relationships and efforts to use psychological treatment strategies.

Standard CBT for depression involves 50-minute weekly, individual psychotherapy sessions and assumes an adequate degree of cognitive functioning such that patients are able to 1) learn and apply new coping skills in the context of sessions, and 2) complete self-monitoring, skills practice, and follow through on experiments and activities between sessions.[60,61] *Yet, given the cognitive sequelae of TBI, patients with TBI and MDD are likely to struggle with the assumptions inherent in standard CBT for depression.* In fact, low adherence rates and feedback from an online CBT study highlighted patients' limitations with reading, comprehension and memory.[32] Notably, the only randomized controlled trial of (standard) CBT for post-stroke depression, another condition with significant cognitive deficits, did not demonstrate superiority of CBT over the control group.[62] However, efforts at adapting CBT to compensate for the neuropsychiatric sequelae of TBI have been beneficial in improving emotional well-being[34] and reducing anxiety in patients with TBI.[63] (See Table 2 for adaptations).

The current protocol will pilot an adapted cognitive behavioral treatment for Major Depressive Disorder for patients who have sustained a moderate to severe TBI. The intervention, CBT-TBI, retains a focus on standard CBT for depression,[60] and adapts it by taking into account the challenges faced by individuals with TBI (e.g., problems with attention, memory, and executive function). The acceptability of the intervention will be examined in open study of 10 subjects, and the potential efficacy of the intervention on depression will be tested in a randomized sample of 40 subjects. The proposed project is the first, necessary step in obtaining funding for an R01 application to conduct a larger, well powered, randomized controlled trial. *If CBT-TBI proves to be effective, it will be one of the first evidence-based psychosocial treatments for MDD following moderate to severe TBI.* If effective, CBT-TBI can eventually be disseminated and used to train clinicians throughout the fields of mental health and rehabilitation medicine, with varying levels of education and experience. Improved treatment of MDD in patients with TBI could lead to significant improvements in overall functioning and reduced burden of disability in the U.S.

PRELIMINARY STUDIES

Past Performance as a Traumatic Brain Injury Model Systems (TBIMS) Site: TBIMS is a longitudinal, multi-center study which investigates the course of recovery and outcomes following acute neurotrauma and inpatient rehabilitation. Spaulding Rehabilitation Hospital (SRH), our primary recruitment site, enrolled patients in the TBIMS National Database from January 1999 through 2007. SRH enrolled a total of 350 subjects into the TBIMS National Database during the 8.75-year period, averaging 40 subjects per year (exceeding the national benchmark of 35 per year). Between January 2002 and September 2007, following expansion of the SRH Brain Injury Unit, the Spaulding TBIMS enrolled 279 subjects into the database, averaging 49 cases per year. After the TBIMS inclusion criteria were expanded to include those injured within 72 hours (previously 24 hours), during the period between January 2006 and September 2007, 100 subjects were enrolled for an average of 57 annually. As a TBIMS National Database Follow-up Center (2007-2011), 345 interviews have been completed, averaging 69 per year. High level performance as a TBIMS Center demonstrates the strong commitment to clinical research and high-volume availability of potential research subjects at SRH. The Spaulding-Harvard TBI continuum of care was awarded the model systems again from 2012-2017.

TBIMS Secondary Data Analysis: The PI examined TBIMS follow up data for participants who completed a measure of depression (PHQ-9) one (n=3,182), two (n=3,142), five (n=2,792), ten (n=1,598), fifteen (n=372), and twenty (n=214) years following their injury.[13] After one year, 28.1% of patients endorsed the presence of 5 or more depressive symptoms at least several days over the last 2 weeks (score of ≥1 on the PHQ-9), with at least one symptom being depressed mood or anhedonia, which was used to indicate the likely presence of MDD. Prevalence of MDD remained relatively stable two (27.8%), five (26.9%), ten (26.3%), fifteen (26.3%), and twenty (24.8%) years post injury. In comparison, only 6.6% of the US population will experience MDD in a given year,[64] highlighting the high rates of depression in individuals who have sustained moderate-severe TBIs. One year following TBI, individuals with depression demonstrate elevated rates of suicidal ideation (31.2%) and suicide attempts (3.5%), which persist after two years (suicidal ideation 21.1%, suicide attempts 2.4%). Thus, there is a critical need for effective treatment of MDD in this population.

INNOVATION

There are no evidence-based guidelines for the treatment of MDD in patients with TBI. Review of pharmacological studies provides some suggested treatment strategies; however, the majority of depressed patients prefer psychotherapy,[65] which is important given that receiving a preferred treatment leads to more clinically meaningful outcomes.[66] As described above, there is insufficient evidence to support clinical practice recommendations for psychotherapeutic interventions for MDD in individuals with TBI.[11,44] Nevertheless, MDD following TBI is highly prevalent and clinicians are forced to rely on evidence from clinical trials that examine treatments for depression in the general population. CBT offers an efficacious treatment for depressed patients without comorbid conditions and preliminary findings suggest that it could be beneficial for patients with TBI. However, Beck initially conceptualized cognitive therapy as a treatment for depressed individuals in the general population. Since its inception, CBT has been adapted for a variety of psychiatric conditions (i.e., suicide, phobias, and personality disorders)[67] and tailored for some difficult-to-treat disorders, such as schizophrenia[68] and adult attention deficit disorder.[69] Successful adaptations of CBT have even been developed for depressed patients with multiple sclerosis,[70] Parkinson's Disease,[71] and Alzheimer's Disease.[72] Yet, CBT for depression has not been adequately adapted for individuals with TBI who are faced with a multitude of specific challenges (i.e., problems with attention and concentration, memory, and executive functioning). *The proposed research is innovative, in that it demonstrates the first, necessary step in developing and prospectively evaluating a cognitive behavioral intervention for MDD that has been adapted for individuals with moderate to severe TBI.* Eventual findings may be used to inform the development of guidelines for depression treatment and inform changes in the standard of care in this population.

II. SPECIFIC AIMS

Aim 1: Manual Development. To develop a structured, cognitive behavioral treatment manual for depression adapted for individuals with moderate to severe traumatic brain injury (CBT-TBI), as well as evaluate its acceptability and tolerability in an open 12-week pilot trial (N=10).

Hypothesis 1a: Participants will report high satisfaction with and acceptability for CBT-TBI per clinical interview and Satisfaction with Therapy and Therapist Scale – Revised (STTS-R).

Hypothesis 1b: Subject adherence to the protocol, *including clinician-rated, self-report, and neuropsychological battery, will be high (at least 80% will complete all sessions).*

Aim 2: To evaluate the acceptability and tolerability of, and adherence to, CBT-TBI in a randomized waitlist-controlled, 12-week pilot trial (N=40).

Hypothesis 2a: Participants will report high satisfaction with and acceptability for the revised CBT-TBI per clinical interview and STTS-R.

Hypothesis 2b: Eighty percent of subjects receiving CBT-TBI will complete the study.

EXPLORATORY AIM

Aim 3: To evaluate the potential efficacy of CBT-TBI for depression in the randomized pilot trial (N=40) and possible moderators and mediators of outcome.

Hypothesis 3a: CBT-TBI will result in a greater decrease in IDS-C scores after 12 weeks (primary outcome) compared to waitlist control.

Hypothesis 3b: CBT-TBI will produce an increase in coping skills, adaptive thinking, positive self-appraisal, social functioning, and activity level compared to waitlist control, and these factors will mediate depressive outcomes.

Hypothesis 3c: Degree of cognitive impairment at baseline will moderate response to treatment.

III. SUBJECT SELECTION

Inclusion criteria:

1. Adults aged 18 and older
2. English language proficiency
3. Ability to provide written, informed consent; OR consent provided by legally authorized representative with assent from subject
4. Ability to see and hear (hearing or visual loss cannot impair ADLs or in-room conversation)
5. Has access to a smartphone/tablet/computer with internet and video capabilities for virtual sessions
6. Having been hospitalized for moderate to severe TBI that occurred at least 3 months prior to study entry
7. Meeting ANY ONE of the following severity criteria, as documented in electronic medical record (EPIC) or available outside records:
   a. GCS 3–12 with GCS motor score ≤ 5 within 4 hours after injury
   b. GCS 3–12 with GCS motor score =6 within 4 hours after injury AND documented intracranial abnormalities on imaging
   c. GCS 13–15 within 4 hours after injury AND documented intracranial abnormalities on imaging
   d. Loss of consciousness (LOC) > 30 min.
   e. Post-traumatic amnesia (PTA) > 24 hours
8. Out of PTA at the time of enrollment (GOAT>75)
9. Clinically significant depressive symptoms: meets criteria for Major Depressive Episode on the MINI or has a total score ≥ 23 on the Inventory of Depressive Symptomatology – Clinician rated (IDS-C)

Exclusion criteria:

1. Uncontrolled medical illness
2. Behavioral dyscontrol, defined as the presence of verbally or physically aggressive behavior in the past month, as evidenced in medical records, pre-screening interviews, or observed by any study staff
3. Presents with PTSD as the primary diagnosis, as determined by a clinician
4. Substance use disorder, moderate or severe, within the past 6 months
5. Has bipolar disorder, a primary psychotic disorder or current psychotic symptoms, or acute suicidality or homicidality
6. Currently receiving regular (≥ 2 times/ mo.) psychosocial treatment for depression
7. Has participated in CBT for depression within the past 6 months
8. Individuals with history of dementia or severe cognitive impairment that is not related to TBI (e.g., cognitive impairment requiring assistance with basic activities of daily living, such as getting ready in the morning)

Recruitment: Subjects will be recruited through a number of sources. Spaulding Rehabilitation Hospital (SRH) will be the main recruitment site.

Outpatient Clinics

The PI obtained commitment from the Director of the Outpatient and Community Brain Injury Rehabilitation Program (Mel Glenn, MD) to support recruitment of depressed patients from the TBI outpatient program. The outpatient clinic screens approximately 200 new patients for TBI evaluations each year, and anecdotal reports from providers suggest that more than half of those patients experience notable depressive symptoms. We will collaborate with the manager and director of outpatient clinics in order to recruit through advertisements, clinicians (physiatrists, physical therapists, occupational therapists, social workers, psychologists), and direct mailings. One strategy includes study staff review of SRH outpatient clinic schedules and Electronic Health Records of current patients in order to identify patients who may be eligible. When potentially eligible subjects are identified via chart review, we will either 1) approach the treating physician about their potential eligibility and then mail an IRB-approved letter signed by the physician or 2) we will mail them a letter directly from the PI to share information about the study. . Clinical staff will obtain verbal consent for interested patients to be contacted by our study staff and may provide information about our study. When possible, a member of our study staff may be on site to share more information about our study with interested patients in person. Finally, we will utilize the Research Patient Data Registry (RPDR) to identify potential subjects across MGB based on key inclusion criteria (e.g., ICD codes indicative of moderate to severe TBI, ICD codes for depressive disorders, age 18 and over) and mail them research invitations, unless they have opted out (in accordance with July 2021 revised MGB policy).

SRH Inpatient Units

Subjects will be recruited from the inpatient brain injury rehabilitation units at Spaulding Rehabilitation Network facilities. Electronic Health Records will be reviewed by study staff to identify potentially-eligible subjects and relevant inclusion/exclusion criteria. Clinical staff will obtain verbal consent for interested patients [or surrogates for inpatient] to be contacted by our study staff and may provide information about our study. When possible, a member of our study staff may be on site to share more information about our study with interested patients in person.

We will plan to attend the Outpatient Brain Injury Advisory Group (OBIAG), the TBI Work Group and other arenas in the hospital where we can address large audiences of clinicians. Using population management tools, we will also ask providers for permission to send mailings to patients. We will concentrate our efforts at Spaulding Rehabilitation Hospital, which is the hub of the Spaulding Rehabilitation Network (SRN), and is located in Charlestown, MA, which is a short distance from MGH and provides a free and easy shuttle service between the facilities. Some subjects will also be recruited from other outpatient clinics in the SRN, located throughout the greater Boston area and the state. Recruitment efforts will expand outside SRN to other Partners and non-Partners institutions who treat patients with TBI.

Some subjects will also be recruited from the pool of callers to the MGH Depression Clinical and Research Program who are interested in research. In addition, we will advertise the study through

internal research listings distributed via e-mail and posted online by MGH, RSVP for Health (a registry run by MGH and the Brigham and Women's Hospital where individuals interested in clinical research can receive information about research studies), a listing on ClinicalTrials.gov, and flyers posted on hospital-approved bulletin boards or in local health clinics. We will also speak with colleagues in the Department of Speech, Language, and Swallowing Disorders, who have occasionally sought CBT services from the PI for patients who are engaged in cognitive remediation. We will also reach out to the Neurology Department at MGH. Finally, we will coordinate with other community organizations to recruit subjects who are not MGH patients, particularly the Brain Injury Association of Massachusetts. We will utilize social media to advertise the study, including Twitter and online forums/groups specifically for individuals with traumatic brain injury. These strategies are intended to publicize the study to as large a group as possible of people who are interested in research, who suffer from the target conditions, and who are likely to be willing and able to come to MGH for the study.

In collaboration with our colleagues at the VA Rocky Mountain Mental Illness Research Education and Clinical Center (directed by Lisa Brenner, PhD), potentially eligible patients will be identified and referred from within the VA Healthcare System. Approval for all recruitment through the VA will be obtained by the VA IRB. We will utilize Electronic Health Record chart review to identify potentially eligible subjects.

Additional subjects will be recruited through our partnership with Community Rehab Care in Watertown, MA (Medical Director, Mel Glenn, MD, Spaulding Rehab). Staff at Community Rehab Care who are briefed on study protocol will gauge client interest in participation and encourage interested clients to contact study staff directly or obtain consent from clients to be contacted by study staff. Study staff will then screen these participants for eligibility. Study clinicians may conduct study procedures (i.e. CBT Treatment, assessment visits) at Community Rehab Care in Watertown, MA in order to minimize participant burden.

Prospective subjects will participate in a brief telephone prescreen by a research coordinator, using the standard prescreening format used by the DCRP with IRB approval plus TBI-related questions, also IRB-approved. The standard prescreen consists of questions about common psychiatric symptoms, comorbidities, psychiatric treatment, and demographic data that would be relevant to the inclusion/exclusion criteria, thus decreasing the likelihood that a patient who clearly does not meet study inclusion/exclusion criteria (e.g., who has been hospitalized for bipolar disorder) will be put to the inconvenience of coming for a screen. TBI-specific questions will relate to the inclusion and exclusion criteria for the study (e.g., degree of severity, diagnosis and timing of TBI). If interested and deemed likely to be eligible, prospective participants will be scheduled for a screening visit in person at the DCRP office.

IV. SUBJECT ENROLLMENT

A total of up to 70 subjects who demonstrate clinically significant depressive symptoms and moderate to severe traumatic brain injury (TBI) will be enrolled in the entire study. A Study Coordinator will determine possible subject eligibility by phone and those that are deemed eligible after the preliminary phone screen will be invited for an screen visit with a DCRP clinician to determine eligibility. The screening visit, which is about 4-6 hours long, will consist

of a meeting with a clinician for a structured diagnostic interview and assessment of depressive severity and neuropsychiatric symptoms, the completion of self-report questionnaires, and neuropsychological testing. This visit may be split into two parts, with the neuropsychological assessment occurring during the second part, in order to accommodate subjects' potential limitations due to fatigue.

In the first phase of recruitment, we will enroll 10 subjects in order to pilot test the newly developed manual in a nonrandomized, open trial. Based on objective and qualitative feedback from participants, the CBT-TBI manual, which includes materials such as CBT homework and study diaries, will then be revised.

Once the CBT-TBI manual has been revised, we will enroll up to 60 subjects in the second phase of recruitment with the goal of randomizing 40 participants. They will be enrolled using the same procedure as described in the open trial (N=10), but eligible participants will be randomly assigned in consecutive order to intervention or waitlist control group. Given that history of pre-injury MDD is the strongest predictor of post-TBI depression[12] and the higher incidence of MDD in women than in men,[73] randomization will be stratified by history of MDD and gender, so that both conditions include the same number of subjects with and without pre-injury MDD, as well as males and females. The randomization list will be provided by the biostatistician and maintained by the research staff. During the first 12 weeks, as per the schedule outlined below, participants randomly assigned to the waitlist control group will be seen only for assessments. Control arm participants will receive treatment as usual outside of our clinic and scheduled assessments in our clinic for 12 weeks. After 12 weeks, they will be offered the CBT-TBI treatment.

Independent evaluators are masters and doctoral-level staff members from the DCRP who donate time to serve as raters for research studies. Full-time psychologists, psychiatrists, and fellows devote 10 hours per week to DCRP research activities, including conducting assessment visits or treatment for studies. Research fellows and advanced practicum students also contribute hours to DCRP research activities as part of their training. DCRP clinicians regularly complete rater trainings for structured diagnostic interviews and measures of depressive severity. DCRP clinicians will be included as study staff and be able to obtain informed consent.

Procedures for obtaining informed consent:

Informed consent will be obtained at the time of the screening visit, prior to the collection of any data for the study (such as questionnaires or diagnostic interview). Before meeting with the study clinician, subjects will receive a written copy of the consent form that includes an easy-to-read description of the protocol, risks and benefits, privacy concerns, and provisions for subjects who decide to discontinue the study. The Study Info sheet will be emailed or mailed to patients on a case-by-case basis as a supplement to consent review, in order to help patients with cognitive impairments process the important information and help them better gauge their potential interest in the study. Subjects will be informed that they may voluntarily discontinue participation in the study at any time. Repetition of consent information can improve subject understanding,[74] which may be particularly important with this population given expected cognitive impairments. A clinician will then review the consent form with the participant and provide the opportunity for the subject to ask questions. The clinician will utilize the University of California San Diego

Brief Assessment of Capacity to Consent (UBACC)[75] to guide his or her assessment of the subject's capacity for consent. All clinicians will be trained in the administration of this measure prior to beginning recruitment. The 10-item scale includes questions about the study that evaluate the subject's understanding, appreciation, and reasoning about protocol elements that are critical to meaningful consent. The UBACC typically takes less than 5 minutes to administer. Each item is scored on a scale of 0 to 2 points, with 0 indicating a clearly incapable response and 2 indicating a clearly capable response. Prior to the start of the study, my mentors and I will prepare a list of answers that will receive a score of 2 on each item. If the subject obtains 2s on all of the items, he/she will sign/date the consent form along with the clinician. If the subject obtains 0s or 1s, the information on the items missed and specific questions will be repeated up to 3 times, consistent with scale administration instructions, in order to clarify any ambiguous or uncertain answers and make a determination about capacity. Consenting clinicians will be encouraged to consult with the PI and her mentors in any questionable cases to determine appropriate action. If it is determined by the consenting clinician that the subject does not have capacity to consent based on inadequate answers to the UBACC, a legally authorized representative may provide written consent along with the subject's assent.

In addition to consent for study participation, subjects will be asked to provide optional consent for audio/video taping of sessions. The purpose of audiotaping, measuring therapist adherence to the treatment manual, will be explained. Subjects who decline consent to audio/video tape will be enrolled in the study and their sessions will not be recorded. Further, subjects will be presented with information about between session contact (for those receiving the intervention), which will be delivered using telephone calls, text message, or email, depending on patient preference. Between session contact utilizing a variety of media will be used with the goal of increasing treatment adherence and engagement. On the consent form, subjects will be asked to list their preferred methods of communication and will be presented with pertinent information about the risks of the various methods of communication. This will be reviewed again at the time of the intervention by the study therapist in order to assure ongoing consent/assent.

Once the consent form has been signed and participants have provided the address at which they will be completing most CBT sessions, study staff will identify the contact information for local law enforcement and emergency services nearest to this address in case of emergency. This information will be stored for quick access in the master log.

V. STUDY PROCEDURES

The primary aim of this study is to develop a highly acceptable, manualized treatment (CBT-TBI) for MDD in patients with moderate to severe TBI. After developing the manual (Phase 1), a nonrandomized trial (Phase 2) will be conducted to test its acceptability and tolerability. Based on objective and qualitative feedback from participants and input from mentors and consultants, the CBT-TBI manual will be revised (Phase 3). We will then pilot test the efficacy of the intervention to reduce depressive symptoms (IDS-C30) after 12 weeks using the revised CBT-TBI manual compared to a waitlist control group in a randomized pilot trial (Phase 4). Once the randomized pilot study is complete, the CBT-TBI manual will be finalized with additional feedback from subjects, mentors, and therapists.

For both phases of recruitment, the same study procedures will be used (unless procedures are modified in Phase 3, which will then be submitted for IRB review). The proposed study involves the following points of contact: (1) Obtaining informed consent and screening (may be broken up into multiple visits), (2) biweekly clinician assessments of depressive and neuropsychiatric symptoms (weeks 2, 4, 6, 8, 10), (3) weekly self-report assessments of depressive symptoms for those receiving the intervention, (4) 12 weekly individual CBT-TBI sessions for those randomized to the intervention, (5) a comprehensive assessment at week 12 (primary endpoint), which includes the neuropsychological battery, and (6) a 3-month follow-up assessment for those who received the intervention (randomized pilot only, phase 4). Assessment visits during the 12 weeks of treatment may be completed by phone. The week 12 visit can be split into two parts, with the neuropsychological assessment occurring during the second part, in order to accommodate subjects' potential limitations due to fatigue.

In the context of the COVID-19 pandemic, all in-person procedures will shift to virtual administration via Zoom videoconferencing and/or telephone. When clinical research is safe to resume in-person, select procedures may occur in office when they are unable to occur remotely. For example, participants who do not have access to a computer may go to the Depression Clinical and Research Program to complete computer-based neuropsychological testing (CNS Vital Signs) on a clinic computer. Parking will be reimbursed per standard Depression Clinical and Research Program protocol if participants park in a designated MGH garage.

The following list includes descriptions of each measure being used in the proposed study.

Screening Measures:
UCSD Brief Assessment of Capacity to Consent (UBACC)[75]: 10 item scale assessing capacity for consent.

Demographics Questionnaire: includes age, sex, gender, ethnicity, education, and employment.

Mini-International Neuropsychiatric Interview (MINI)[76]: A brief structured diagnostic interview permitting rapid diagnosis of major psychiatric disorders.

Ohio State University TBI Identification Method – Interview Form[134]*:* A brief interview form for obtaining TBI history and severity.

SCID Psychiatric History: A brief, semi-structured interview form for obtaining basic psychiatric history.

Galveston Orientation and Amnesia Test (GOAT)[77]*:* A measure of orientation to place, time, and personal information used to assess post-traumatic amnesia.

Cognitive Therapy Awareness Scale (CTAS)[78]: A 40-item, self-report, true-false measure of knowledge of basic CBT skills. The CTAS is a simple, brief measure that has been used in a number of studies.[78,79,80,81] A score of 20 is suggested to be the average score obtained by individuals with no awareness of cognitive therapy.[82]

Substance Use Questionnaire: A 15-item, self-report questionnaire that assesses if the patient used psychoactive substances in the last 30 days.

The Alcohol Use Disorders Identification Test: A 3-item, clinician-rated measure of alcohol consumption that can help identify individuals who are hazardous drinkers or have active alcohol use disorders.[83]

PROMIS Pain Intensity: Measures how much a person hurts.[84]

PROMIS Pain Interference: Measures consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities.[85]

Depression Measures:
Inventory of Depressive Symptomology (IDS-C30)[86] (primary outcome): 30-item clinician rated scale that assesses severity of depression according to the nine DSM-IV[51] symptom domains.

Quick Inventory of Depressive Symptomatology, Clinician-Rated (QIDS-C)[87]: 16-item clinician-rated scale that assesses severity of depression according to the nine DSM-IV[51] symptom domains.

Columbia-Suicide Severity Rating Scale (C-SSRS)[88]: Clinician assessment of recent through lifetime suicidal ideation and behavior (i.e., attempts, interrupted and aborted attempts, preparatory behavior, and nonsuicidal self-injury).

Beck Depression Inventory II (BDI-II) [89]*:* A 21-item self-rated questionnaire that assesses severity of depression.

Hospital Anxiety and Depression Scale (HADS) [90]*:* A 14-item self-rated questionnaire that assesses severity of anxiety and depression.

PROMIS Bank v1.0: Depression: A 28 item, self-rated, Computerized Adaptive Test that assesses severity of depression. The first item is fixed for all participants, but participants' response will determine which item is selected next by the program; this is repeated for all subsequent items.

Modified Beck Hopelessness Scale[135]: A self-report measure of negative expectations for the future that has been modified from the 20-item BHS [136]. The 10-item modified BHS uses a 5-point Likert scale, ranging from 0 (not at all) to 4 (very much), with total scores ranging from 0 to 40.

Neurological Measures:
Information about TBI diagnosis and severity will be obtained via interview and review of medical records (i.e., duration of unconsciousness, Glasgow Coma Scale (GCS)[91] score, duration of posttraumatic amnesia (PTA), neuroimaging results, and inpatient and/or outpatient rehabilitation services). A Release of Information will be obtained at the screening visit in order to access the subject's medical records.

Neuropsychological Measures:
Rivermead Postconcussion Symptom Questionnaire (RPQ)[92]: A self-report questionnaire that assesses presence and severity of somatic, cognitive, and emotional symptoms after TBI.

Wechsler Adult Intelligence Scale IV (WAIS-IV): Similarities and Digit Span subtests[93]: The WAIS-IV is a standardized neuropsychological test battery designed to assess cognitive ability

and intelligence. The selected subtests assess verbal comprehension, working memory, and processing speed.

Test of Premorbid Functioning (TOPF)[94]*:* A standardized neuropsychological test that estimates an individual's premorbid cognitive and memory functioning.

Wechsler Memory Scale IV (WMS-IV), Logical Memory subtest[95]*:* A subtest of the WMS-IV designed to measure immediate, delayed, and auditory aspects of memory.

CNS Vital Signs: Brief, computerized, remotely administered neurocognitive test battery comprised of seven "core" subtests and three "optional" subtests measuring memory, reaction time, processing speed, executive functioning, attention, cognitive flexibility, social perception and aspects of cognition. The measures have been normed, and validity and reliability has been demonstrated in peer-reviewed publications since 2006[96].

Neuro-QOL Item Bank v2.0 Cognition Function Short Form[97]: An 8-item, self-rated questionnaire assessing cognitive function.

Measures of Global Outcome:
Glasgow Outcome Scale (GOS-E)[98]*:* A clinician-administered tool that assesses global functioning after brain injury using a structured interview and assigns an individual to one of eight functional categories, ranging from 1 (dead) to 8 (upper good recovery).

Measures of Social Functioning:
Neuro-QOL Item Bank v1.0 – Ability to Participate in Social Roles and Activities Short Form: An 8-item scale that assesses perceived ability to perform one's usual social roles and activities.[99]

Neuro-QOL Item Bank v1.1 –Satisfaction with Social Roles and Activities Short Form: An 8-item scale that assesses satisfaction with performing one's usual social roles and activities.[100]

Measures of Emotion Regulation:
NIH Toolbox Anger-Affect Fixed Form: A 5-item self-rated questionnaire assessing the patients' experience of anger.[100]

Neuro-QOL Item Bank v1.0 Emotional and Behavioral Dyscontrol[101]*:* An 8-item self-rated questionnaire assessing the patients' experience of emotional and behavioral dyscontrol.

Automatic Thoughts Questionnaire-Revised (ATQ-R) [102]*:* A 40-item self-rated questionnaire that assesses the frequency with which an individual endorses positive and negative self-statements.

Measures of Coping and Awareness:
Coping Attitudes Scale (CAS)[103]*:* A 23-item, self-report measure of positive attitudes, reflective of patients recovered from depression.[104]

Awareness Questionnaire (AQ)[105]: A 17-item measure of impaired self-awareness with patient and family member forms.

NIH Toolbox Item Bank v2.0 Meaning and Purpose[101]*:* An 8-item self-rated questionnaire assessing the patients' feelings of meaning and purpose.

Measure of Activity: Each participant will be provided with an activity tracker while receiving the intervention (e.g. Fitbit Charge 3™, Fitbit Charge 4™,or a pedometer-like device) which will measure number of steps walked as an index of behavioral activation. Devices will be wireless-enabled and will sync to a computer, allowing for real time, quality controlled access to data. Patients will be provided with the device at the first psychotherapy visit (week 1). Behavioral

treatment adherence data from the activity trackers will be downloaded weekly and used to inform treatment. Specific information about the devices will be submitted to the IRB once it is obtained.

Acceptability and Satisfaction:
Satisfaction with Therapy and Therapist Scale – Revised (STTS-R)[106]*:* A 12-item self-rated questionnaire assessing the satisfaction with the therapy and therapist.

Working Alliance Inventory (WAI)[107]*:* A clinician-rated and a self-rated 12-item questionnaire assessing the alliance between the clinician and patient.

Post Treatment Visit Assessment: A brief survey assessing the perceived helpfulness of the subject matter discussed at each treatment visit.

End of Treatment Assessment: A brief survey assessing the feasibility and perceived helpfulness of the intervention.

Other:
Epidemic – Pandemic Impacts Inventory (EPII) [108]: a newly developed measure designed to learn about the impact of the coronavirus disease pandemic and future epidemics and pandemics on various domains of personal and family life.

All data will be entered directly into REDCap by the study clinicians and subjects. Completion of web-based, self-report measures via computer or tablet is likely to be more appealing to the study population who may experience physical injuries that impact writing abilities. Further, use of REDCap will likely minimize missing self-report study data and allow for immediate follow up on missing items, which is likely to be relevant for individuals who have sustained TBIs and frequently experience problems with attention and concentration. In the event that circumstances inhibit the ability to directly enter the data electronically (via computer or tablet), paper copies will be provided for clinician-rated or self-report administration. These paper copies will be directly downloaded from REDCap to ensure that the measures look identical to the electronic copies.

Table 1 below outlines the schedule of assessments for each phase of the study

Table 1: Schedule of Assessments for Active CBT Patients

Assessment	Screen	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12 / Last Visit	3mo F/u
Informed Consent; UBACC	X													
Inclusion/Exclusion Criteria	X													
Demographics/ Contact Information	X													
Clinician Administered Psychiatric History Form	X													
OSU TBI Form	X													
Release of Information	X													
GOAT	X													
MINI	X													
C-SSRS	X												X	X
AUDIT-C	X													
Substance Use Questionnaire	X													
Concomitant Treatment Log	X		X		X		X		X		X		X	X
Adverse Events			X		X		X		X		X		X	X
CTAS	X												X	X
IDS-C	X												X	X
GOS-E	X												X	X
QIDS-C			X		X		X		X		X			
PROMIS Depression	X		X		X		X		X		X		X	X
BDI-II	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HADS	X												X	X
RPQ	X						X						X	X
Neuropsych Battery (see separate table for individual tests)	X												X	
Neuro-QOL Cognition Function – SF	X												X	X

Anger-Affect Fixed Form	X						X						X	X
Neuro-QOL Ability to Participate in Social Roles and Activities-SF	X						X						X	X
Neuro-QOL Satisfaction with Social Roles and Activities-SF	X												X	X
Neuro-QOL Emotional and Behavioral Dyscontrol-SF	X												X	X
Coping Attitudes Scale	X						X						X	X
Awareness Questionnaire (patient)	X												X	
NIH Toolbox Meaning and Purpose	X						X						X	X
ATQ-R	X						X						X	X
Activity Tracker (data syncs wirelessly)			X	X	X	X	X	X	X	X	X	X	X	
WAI-SF							X (patient version only)						X	
PROMIS Pain Intensity	X						X						X	X
PROMIS Pain Interference	X						X						X	X
Beck Hopelessness Scale	X												X	X
STTS-R and interview													X	
Post treatment assessment (participant)		X	X	X	X	X	X	X	X	X	X	X		
Homework Compliance (therapist)			X	X	X	X	X	X	X	X	X	X	X	
End of Treatment Feedback													X	
COVID-19 Supplemental Survey	X												X	X
Approximate Time Estimate	240 min	< 10 min	30 min	< 10 min	30 min	< 10 min	45 min	< 10 min	30 min	< 10 min	30 min	< 10 min	180 min	60 min

Table 2. Schedule of Assessments for Waitlist Patients (note: after WL week 12 patients continue with Active CBT Assessments for 12 weeks)

Assessment	Screen	WL Wk 2	WL Wk 4	WLWk 6	WL Wk 8	WL Wk 10	WL Wk 12 / Last Visit
Informed Consent; UBACC	X						
Inclusion/Exclusion Criteria	X						
Demographics/ Contact Information	X						
Clinician Administered Psychiatric History Form	X						
OSU TBI Form	X						
Release of Information	X						
GOAT	X						
MINI	X						
C-SSRS	X						
AUDIT-C	X						X
Substance Use Questionnaire	X						
Concomitant Treatment Log	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
CTAS	X						X
IDS-C	X						X
GOS-E	X						X
QIDS-C		X	X	X	X	X	
PROMIS Depression	X	X	X	X	X	X	X
BDI-II	X						X
HADS	X						X
RPQ	X						X
Neuropsych Battery (see separate table for individual tests)	X						X

Neuro-QOL Cognition Function – SF	X						X
Anger-Affect Fixed Form	X						X
Neuro-QOL Ability to Participate in Social Roles and Activities-SF	X						X
Neuro-QOL Satisfaction with Social Roles and Activities-SF	X						X
Neuro-QOL Emotional and Behavioral Dyscontrol-SF	X						X
Coping Attitudes Scale	X						X
Awareness Questionnaire (patient)	X						X
NIH Toolbox Meaning and Purpose	X						X
ATQ-R	X						X
PROMIS Pain Intensity	X						X
PROMIS Pain Interference	X						X
Beck Hopelessness Scale	X						X
COVID-19 Supplemental Survey	X						X
Approximate Time Estimate	240 min	30 min	30 min	30 min	30 min	30 min	120 min

Table 3. Schedule of Neuropsychological Assessments for Open Trial (Phase 2) and Randomized Pilot Study (Phase 4)

Assessment	**Screen**	**Week 12 / Last Visit**
WAIS-IV Similarities	X	
WAIS-IV Digit Span	X	X
Test of Premorbid Functioning (TOPF)	X	
WMS-IV Logical Memory	X	X
CNS Vital Signs	X	X
Estimated time	1.5 hours	1 hour

Randomized Pilot Study (Phase 4): Individuals who are randomized to the wait-list control arm will be offered the opportunity to receive 12 weeks of CBT-TBI after they complete the week 12 visit. They will not receive additional compensation if they opt to receive the intervention.

Study Intervention

Study Therapists and Training: Clinicians at the DCRP, including Dr. Fisher, will administer the treatment protocol. Therapists will be required to have a master's degree and will be supervised and trained by Drs. Pedrelli and Fisher.

Treatment Fidelity: Recommendations suggested by the NIH Behavior Change Consortium workgroup on treatment fidelity will be implemented.[109] Therapists will be trained on the treatment, and adherence to the manual will be monitored. When participants provide consent, sessions will be audiotaped in order to facilitate supervision and manual adherence by Dr. Pedrelli and the PI. Weekly supervision with study therapists includes regular review of session recordings and feedback on adherence to the manual.

Content of the Treatment (CBT-TBI):

Introduction *(Sessions 1-2).* A gradual introduction to treatment with strong emphasis on rapport building, given that participants will likely have cognitive deficits (and some might have deficits in social cognition or a degree of paranoia[54]). Emphasis on psychoeducation about depression after TBI, as well as the CBT model.

Behavioral Techniques *(sessions 3-4),* including: 1) Symptom self-monitoring. 2) Introduction to behavioral activation and identifying strategies to increase engagement with outside world. Increased interactions with family and friends may create opportunities for positive social experiences and foster a sense of belonging in one's environment, which may help to improve depression.[110] 3) Collaborative identification of SMART goals (Specific, Measurable, Achievable, Realistic and Relevant, Time Limited) broken down into achievable components.[111] A problem solving approach will be used to address possible barriers to achieving goals.[112] 4) Aspects of social skills training[113] will be used to address interpersonal and communication difficulties.

Cognitive Techniques *(sessions 5-7).* The cognitive model will be illustrated with concrete examples reviewed multiple times. Strategies to identify cognitive distortions, challenge negative thoughts, and develop rational responses will be reviewed and simple thought records will be used. Cognitive restructuring will help patients challenge negative beliefs that maintain their depression and develop more realistic, adaptive ways of thinking.[94] We will elicit patients' automatic thoughts about their injury. For example, catastrophizing and demoralization about current inadequacies are often observed in depressed stroke patients who frequently compare current functioning with pre-stroke level of functioning.[114] We will work with patients to identify similar distortions and on learning to accept and adjust to life after their injury, while learning to identify their values. Research has shown that increased sense of meaning in life is associated with lower levels of depression.[115]

Combining Techniques/Coping Skills *(sessions 8-11)*. Focus on integrating concepts via practice, repetition, and specific techniques: 1) Behavioral chain analysis to promote the relationship between one's thoughts, feelings, and behaviors. Facilitates conceptualization of target problems, identifies gaps in skills, provides opportunity for discussion of adaptive coping skills, and facilitates engagement in treatment.[116] 2) Identification of behavioral coping strategies that can be used when the patient identifies unhelpful thoughts or urges to act aggressively or

respond impulsively, such as habit reversal centering on a competing response (e.g., fold your hands together and squeeze them so you can't use them) or stimulus control strategies (e.g. play a musical instrument, reminder notes) which are often useful for patients with impulse control disorders.[117] By facilitating adaptive coping skills, the therapist can help minimize the psychological effects of stressful events that contribute to depression.[118,119] 3) Behavioral experiments as a vehicle for new learning and belief appraisal,[120] particularly when addressing difficulties with adjustment and changes in identity.[121]

Summary, Review, and Relapse Prevention *(session 12)*: Summary of progress, with emphasis on recognizing and responding to signs of relapse. Discussions about further treatment planning, when applicable. Some assistance with referrals for further treatment may be provided. No follow up care will be provided at the DCRP.

Strategies for Tailoring the Treatment include: 1) between session check-ins (via phone, text message, or email) to monitor progress on goals, provide homework reminders, troubleshoot barriers, 2) flexible length of weekly sessions (60 min or less), 3) focus on 1-2 key concepts per session, emphasizing repetition and checks for understanding, 4) written session summaries, 5) therapeutic use of baseline neuropsychological assessment, 6) use of patient workbook, 7) external memory compensations (i.e., calendar, notebook), and 8) inclusion of support person, if applicable (see details in Table 2).

Table 2. Strategies for Tailoring the Treatment

Adaptation	Details	Impairment Addressed	Rationale
Length and structure of treatment	• 12 weekly individual sessions, up to 60 min. each (shorter if needed) • Focus on 1-2 key concepts per session, emphasizing repetition and checks for understanding.[122]	Information processing; Memory impairment; Attention deficits	Studies of CBT for depression include similar number of sessions.[62,123] Treatments of similar length showed improvement in symptoms of anxiety[63] and depression[35,50] in TBI patients.
Between session 'check-ins'	• 2 contacts, occurring every 2 days (±1 day to account for weekends) delivered in various formats depending on patient preference: phone, text message, email, etc. • Monitor progress on goals, provide homework reminders/prompts, troubleshoot barriers	Memory; Executive function	Reinforces concepts reviewed in session. Troubleshooting allows sessions to be more efficient. Use of electronic memory aids has been beneficial in improving memory deficits for TBI patients engaged in neuropsychological rehabilitation.[124,125]
Session summaries	• Written plan summarizes main concepts covered; outlines work for upcoming week, compensatory strategies to be used and details of between-session reminder(s).	Recall; Information Processing; Impaired Learning	Modeling what is required for successful homework completion can be a successful strategy to enhance executive function.[126]
Therapeutic Use of Baseline Neuro-	• Results from neuropsychological testing will be compiled for the therapist prior to the treatment in order	Memory impairment; Executive function;	Allows compensatory strategies to be individually tailored to each participant and maximizes real-world validity, as

psychological Assessment	to inform the selection of individualized strategies	Information Processing speed; Attention/ Concentration; Social Cognition	opposed to providing a "one-size-fits-all" manual. Adaptations utilized in a previous trial of CBT for the treatment of emotional distress after acquired brain injury.[34] Will utilize strategies that have been successfully employed with adults with attention deficit hyperactivity disorder (ADHD).[69]
Individually tailored compensatory strategies	• With input from mentors and didactics, a list of strategies will be included in the manual; therapists are also encouraged to develop strategies with each patient. • Examples: audiotape sessions, reminder/prompting system (i.e., alarm), rehearsal, carry index card in wallet, post it note on mirror		
Provide patient workbook	• Includes numerous handouts with key information and summaries. Wherever possible, handouts include options for selection rather than blank spaces	Learning Executive Function	Helps participants remain organized. Handouts with options minimize the extent to which patients must rely on their ability to generate new ideas and rely on memory of strategies.
External memory compensations	• Such as notebooks and calendars	Memory impairment	Useful strategies for patients with TBI and memory problems,[127] as well as adults with ADHD.[69]
Include support person (when possible)	• Helps with treatment planning and carrying out homework assignments	Impaired insight Problems with generalization	Increased repetition/prompting likely to improve self-awareness, follow through and generalization of skills

VI. BIOSTATISTICAL ANALYSIS

Preliminary analyses will describe the participants' sociodemographic and clinical characteristics. Comparisons will be made using Mann-Whitney or chi-square tests to determine if the randomization provided a balanced sample and if patients who dropped out differ from those who did not. All analyses will be conducted using the SPSS and/or Stata statistical packages.

Aim 1 (Manual Development and Acceptability and Tolerability in Open Trial): We will use descriptive statistics to report the number of intervention sessions attended (we expect > 80%), number of assessment sessions attended (we expect > 80%), number of study completers (we expect >80%), and rate of satisfaction with treatment (total STTS-R score).

Aim 2 (Acceptability, Tolerability, and Adherence in Randomized Trial): We will use descriptive statistics to report the number of intervention sessions attended (we expect > 80%), number of participants recruited per month (we expect 3/mo), randomization rate (number randomized/number consented; we expect about 67% of those consented will be randomized), number of assessment sessions attended (we expect > 80%), retention (number of study completers/number randomized; we expect >80%), and rate of satisfaction with treatment (total STTS-R score).

EXPLORATORY AIM

Aim 3 (To evaluate the potential efficacy of CBT-TBI for depression in the randomized pilot trial (N=40) and possible moderators and mediators of outcome):

Hypothesis 3a: CBT-TBI will result in a greater decrease in IDS-C scores after 12 weeks (primary outcome) compared to waitlist control. Response over 12 weeks defined by 50% or greater decrease on IDS-C total; remission ≤6 on IDS-C total. Continuous variables will be analyzed by generalized mixed effect modeling, which impute missing values based on maximum likelihood estimates of missing parameters, allowing analysis of all participants. A time-by-condition interaction will be analyzed to test the intervention's efficacy. Relevant potential covariates (e.g., caregiver presence) will also be examined. The percent of responders and remitters in each group will be computed in order to estimate an effect size for the R01. Although I will test for statistical significance, the primary aim of this pilot RCT is to estimate the intervention's effect size to conduct a larger, more adequately powered R01 study, as is outlined in NIH guidelines for developing behavioral interventions[128]. Given that some prior studies utilizing CBT in patients with TBI suggest large effect sizes for reducing emotional distress and depressive symptoms,[32,34] we expect similar findings.

Hypothesis 3b: CBT-TBI will produce an increase in coping skills, adaptive thinking, positive self-appraisal, social functioning and activity level compared to waitlist control, and these factors will mediate depressive outcomes. To evaluate the indirect effect of CBT-TBI to depression (IDS-C) through coping skills, adaptive thinking, positive self-appraisal, social functioning, and activity level, we will employ an SPSS macro (PROCESS) to test the significance of the indirect effect with a bootstrapping approach to obtain confidence intervals.[129] The constructed conditional process model proposes that CBT-TBI will lead to increased coping skills, adaptive thinking, positive self-appraisal, social functioning and activity level, and that increase in these mediators will result in reduced depression. Bootstrapping is superior to other methods for determining the significance of indirect effects, as the assumption of normality for the sampling distribution is not required and power is improved.[130]

Hypothesis 3c: Degree of cognitive impairment at baseline will moderate response to treatment. We will run a hierarchical regression model. The main predictor variables (CBT-TBI, cognitive impairment) will be mean centered based on previous research.[131] Their interaction will then be entered to examine the moderating effect of cognitive impairment on the relationship between CBT-TBI and depression after entering the covariates (i.e., caregiver presence). To examine the moderation hypotheses, we will employ an SPSS macro (MODPROBE) to test whether there is a significant interaction.[132]

VII. RISKS AND DISCOMFORTS

There are some potential risks and burdens to participating in the study. Risks and discomforts associated with receiving psychotherapy are generally considered modest, but can include a worsening of psychiatric symptoms as well as psychological discomfort associated with discussion of one's difficulties. Patients will be given telephone numbers of the doctors involved in the study if they would like to talk about any discomforts. Second, answering detailed questionnaires and completing neuropsychological testing may create a mild degree of inconvenience for the subjects, and attending individual sessions plus rater assessments may be seen as time-consuming and inconvenient. For study visits involving assessments and not

treatment, we have provided compensation for subjects' time, commensurate with hourly compensation for non-treatment studies being conducted at the DCRP. Third, a general risk associated with treatment for depression includes the risk that depression may not respond to treatment. Subjects will be informed of all of the aforementioned risks during the consent process.

VIII. POTENTIAL BENEFITS

It is possible that the participants may not receive any direct benefit other than a detailed psychiatric evaluation. However, it is hoped that the intervention could provide relief from depressive symptoms and improve the level of functioning exhibited in some participating patients with TBI and MDD.

Subjects participating in this study may experience individual benefits from receiving the intervention. The intervention, which will be conducted by a master's or doctoral-level clinician, will be provided to the participants at no charge. Subjects will receive $40 for completion of the entire screen visit and $30 each for completion of the endpoint and 3 month follow up visits. If patients do not complete the entire screen visit due to ineligibility, they will receive $20 to cover the cost of transportation. If patients complete the entire screen, but are deemed ineligible after the visit based on their medical records, the patient will receive $40 to compensate for their travel and time spent in our clinic. Patients will not be compensated for treatment sessions. Patients who complete the 12-week study will have the option of keeping the Fitbit Charge 3 activity tracker (valued at $150 retail) or Fitbit Charge 4 (valued at $130 retail) for their personal use. This compensation was chosen after consultation with the director of the Depression Clinical and Research Program (DCRP) to be consistent with the compensation for non-treatment studies at the DCRP.

Benefits to future patients, researchers and clinicians could include the development of more effective treatment for major depressive disorder experienced by individuals who have sustained a moderate to severe traumatic brain injury.

IX. MONITORING AND QUALITY ASSURANCE

Data Safety

The principal investigator and study staff will review all Adverse Events (AEs) and Serious Adverse Events (SAEs) experienced by subjects and report them to the IRB according to the guidelines for Adverse Event Reporting. "Serious adverse events are events that result in any of the following outcomes: death; a life threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect. In addition, events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above." SAEs will be discussed with Dr. Fisher's primary mentor and co-mentors.

Notification will be sent to the IRB by phone, email or a fax transmittal of the report within 24 hours of the SAE's occurrence. The sponsor will be notified according to its regulations

governing SAE reporting. Relevant information regarding the SAE will be included in this report, including information about the event and its outcome, the history of all study interventions, all concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. This information will be expeditiously reviewed and the possible relevance of the SAE to the study intervention will be assessed.

Data Monitoring

All data will be entered into REDCap directly by subjects and clinicians via computer or tablet. Use of REDCap will likely minimize missing study data and allow for immediate follow up on missing items, which is likely to be especially pertinent to the study population, many of whom will experience problems with attention and concentration.

To insure the usability of self-report data, the research coordinator will review all self-report measures to insure their completeness. The PI (or, in rare cases, her designee) will review all self-report assessment forms and clinician-administered instruments within one week of their completion to assure that they are being completed correctly. Any errors in completion will be reviewed to determine if directions or procedures for the assessments need to be altered. In this case, permission from the IRB will be requested to change any procedure. The intervention sessions are also audiotaped and a random selection rated for competence and adherence to the protocol. This will also insure the usability of the data.

In addition, a data safety monitoring board will be assembled prior to the start of the study. This will consist of at least three staff-level investigators, independent of the current group of mentors; one will have expertise clinical interventions with individuals who have sustained a traumatic brain injury; the second will have expertise in clinical trial design; the third will serve as a statistical consultant. The DSMB will meet at least quarterly per year to review study progress, address any difficulties with recruitment, and address any safety related matters that may arise. Details of the logistics of the DSMB are as follows:

a. **Unblinded Reporting** – Safety information for this study will be reported to the DSMB in an unblinded manner.

b. **Range of Safety Reporting to the DSMB** – It is considered necessary for the purpose of monitoring the safety of the study that the DSMB review not only adverse events (AEs) and serious adverse events (SAEs), but other data that may reflect differences in safety between treatment groups. This includes treatment retention rates and reasons for drop-out.

c. **Serious Adverse Events** – Expedited review will occur for all events meeting the FDA definition of SAEs –

i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly. This also includes any event that a study investigator or the DSMB judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs will be required to be reported to the DSMB, regardless of any judgment of their relatedness to the study intervention. All relevant information will be reported to the DSMB for each SAE including information about the event and its outcome, concomitant medications, the subject's medical history and current conditions, and all relevant laboratory data. Notification by e-mail, and FAX transmittal of all related study forms shall be made to the DSMB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study intervention. Additional reporting to local IRBs will be done

within 24 hours of the SAE. Reporting to the NIH will be made according to their respective regulations governing SAE reporting.
d. **Non-Serious Adverse Events** – At periodic intervals (quarterly during the course of the study and then again at its completion), the DSMB will be provided with un-blinded summaries of the numbers and rates of adverse events by treatment group. These reports will include types of events, severity, and treatment phase.
Data on individual non-serious adverse events is not expected to be needed for this review.
e. **Other Safety-Related Reports** – At twelve-month intervals throughout the course of the study, the DSMB will also receive unblinded summary reports of treatment retention and reasons for drop-out, by treatment arm and study phase.
f. **Study Stopping Rules** – If at any time during the course of the study, the DSMB judges that risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

Digital Monitoring Device Data Collection:
Phase I: Data collected from the current study will not be sent to research collaborators outside of Partners.

Phase II: Partners investigators will not send research data outside of Partners. Use of Fitbit necessitates collection of digital monitoring device (DMD) data through the Fitbit application. Study staff will set up deidentified accounts for all participants in the Fitbit group. Account set up requires entries in fields for first and last name, and we will use "Participant" in the first name field and a de-identified component of the participant's last name in the last name field. Account set up also requires entry of approximate height and weight (self-reported by the participant) and birthday. To deidentify birth dates, we will standardize approximate birthdays as the first day of the month and year of the participant's birth. Participant DMD data will be processed securely though the Fitbit data collection company, Fitabase. Fitabase does not store identifiable data and all data synced from the Fitbit is uploaded through encrypted server communication and stored in a highly secure infrastructure.

Zoom Videoconferencing for Completion of Virtual Procedures:

A Partners Enterprise Zoom account will be used for all study visits. Zoom links will be provided directly to study participants before treatment or assessment sessions. The waiting room will be enabled, and the meeting will be locked once all participants have entered. Participants will be provided with written guidelines and recommendations for all videoconferencing sessions (e.g., use in a private, secure area).

X. REFERENCES

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