Study Protocol

Study Title:
Augmenting Hospitalization for Serious Mental Illness: Cognitive Bias Modification

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Detailed Protocol

PRINCIPAL/OVERALL INVESTIGATOR
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PROTOCOL TITLE
Augmenting hospital care for SMI by targeting interpretation bias

This study will be linked to an existing protocol entitled "Establishing the Effectiveness of Cognitive-Behavioral Partial Hospitalization for Anxiety, Depression, and Overall Functioning" (# 2010-P-001047/6)

VERSION DATE
June 8th, 2021

BACKGROUND AND SIGNIFICANCE
There is an urgent unmet treatment need for individuals with Serious Mental Illness (SMI). NIMH Strategic Objective 4 states that the "chronic disability an*d early mortality of Serious Mental Illnesses (SMI)...demand a rapid response*." Over 4% of the adult US population has a SMI, defined as a mental disorder associated with significant functional impairment[1]. SMI spans diagnostic categories, including individuals with a range of mood and anxiety disorders, among others. Individuals with SMI die 10-32 years prematurely[2], and are almost 13 times more likely to die by suicide[3]. Hospitalization is common among those with SMI, with 9% estimated to have received inpatient care in 2014[1], not including partial hospital and residential levels of care. Hospital stays are typically brief, and residual symptoms upon discharge predict relapse and re-hospitalization[4–7]. Moreover, hospitalized patients often exhibit residual cognitive and functional impairments, despite symptom improvement[8]. The months following discharge from hospitalization are risky, as individuals transition from a highly structured and supportive environment to home, acute stressors, and uncertain aftercare. Interventions that efficiently accelerate improvement are urgently needed to reduce residual symptoms upon discharge and ultimately risk of rehospitalization. Ideally, augmentation strategies need to be reliably and easily delivered both in the hospital and continued during the transition to outpatient care.

Interpretation bias is a crucial transdiagnostic target. Daily life constantly requires the resolution of ambiguity. For example, not getting a job or a friend not returning a call can be interpreted in multiple ways. The way in which individuals automatically resolve the countless ambiguous situations encountered each day has a large impact on their affect and behavior. Interpretation bias, the tendency to resolve ambiguity negatively, is a crucial therapeutic target due to its causal maintaining role in emotional disorders[9,10]. Interpretations are made both "*on-line*" the moment an individual encounters ambiguity and "*off-line*" during retrieval of a memory for the event. Theoretical models propose that interpretation bias maintains a vicious cycle in which an individual experiences the world as more hopeless or threatening, which heightens negative affect, increases behavioral avoidance and more biased cognition (e.g., [11,12]). Interpretation bias maintains psychopathology not only due to its direct effect on affect, but also through cascading and interacting effects with other cognitive processes[13,14], contributing to a pervasive maladaptive cognitive style. Individuals with this cognitive vulnerability have difficulty generating multiple interpretations for ambiguous situations, more easily get "stuck" in repetitive negative thinking, have poor emotion regulation, and more suicidal ideation (see [15]). In a psychiatric hospital sample, interpretation bias was a better predictor of suicidal ideation at discharge than any other demographic or clinical variable available (see preliminary studies). Moreover, interpretation bias upon admission prospectively predicted treatment response.

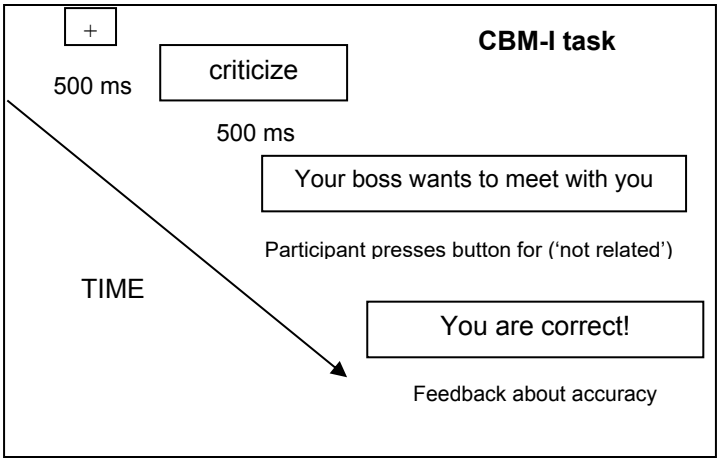
Interpretation bias is an important mechanism across species and diagnoses.

1) Animals in stress and depression-like states exhibit interpretation bias[16,17].
2) Self-report, reaction time, behavioral, and neurophysiological measures of interpretation bias correlate with psychopathology (Major Depressive Disorder (MDD)/dysphoria[18–22]; anxiety[15,23,24]; ruminators [21,22]; Bipolar Disorder[25]; e.g., *Interpretation bias explained 20% to 30% of symptom variance in individuals with MDD*[18]).
3) Interpretation bias is a risk factor for developing psychopathology.
   - Children at familial risk for mood disorders exhibit interpretation bias[26] .
   - Interpretation bias prospectively predicts depressive symptoms in adults[27].
   - Inducing a negative bias in healthy individuals leads to impaired emotion regulation[28].
   - Interpretation bias better predicts avoidance behavior than self-report symptom measures[29].
   - Experimentally modifying interpretation affects other cognitive biases (attention[14], memory[30,31], imagery[32]), emotion regulation (attentional control and worry[33], rumination[34], intrusive memories[35]) and clinical symptoms when delivered over multiple sessions[36,37].
4) Interpretation bias influences treatment outcome.
   - Baseline level of interpretation bias predicts treatment response in SMI (see preliminary studies).
   - Change in interpretation bias mediates symptom improvement in treatment [38,39,40–42].
   - Rate of change in negative cognitions early in psychotherapy predicts overall symptom change[43].
   - Successful reduction of interpretation bias leads to continued symptom improvement[44].

Given the wealth of data linking interpretation bias to psychopathology across diagnostic categories, engaging this target is consistent with the RDoC framework. Interpretation bias is linked to several RDoC constructs,[45] primarily within the Negative Valence domain (rumination, worry, attentional bias, hopelessness, interpretation of facial expressions, risk assessment, avoidance behavior, memory retrieval). Interpretation bias has been validated as an important mechanism across multiple units of analysis and translationally across animal and human models. Targeting interpretation bias has positive effects on behavior, cognition, and clinical symptoms.

CBM-I is a simple, efficient, and effective, method to engage interpretation bias.

The current proposal aims to develop an efficient and scalable method for engaging interpretation bias to improve outcomes during and following hospitalization. Cognitive bias modification tasks targeting interpretation bias (CBM-I) are low-intensity, computerized interventions that facilitate a more adaptive interpretive style via repeated practice on a training task. Importantly, the CBM-I task proposed here aims to engage interpretation bias in an "on-line" manner - the moment of encountering ambiguity - which more closely matches the manner that interpretation bias naturally operates and may not require as much insight as alternative methods. The proposed intervention, called **HabitWorks**, uses a **Word-Sentence Association Paradigm (WSAP**[23,41]) to reinforce an adaptive interpretation style. Specifically, this task presents a word representing either a negative or benign interpretation *("criticize"* or *"praise")* of an ambiguous sentence that follows *("Your boss wants to meet with you")*. Individuals then indicate by button press if they think the word is related to the sentence. The feedback, "*You are correct!*" is displayed if they endorse benign interpretations or reject negative ones (Figure 1). This task taxes



attentional control and working memory to remember the word that flashes and make the relatedness judgment. Participants complete the task as quickly and as accurately as possible, thereby prompting more automatic responding.

Preliminary studies suggest that CBM-I is more efficient and effective at engaging interpretation bias than CBT[55]. Thus, CBM-I may be particularly useful in brief treatment settings, such as psychiatric hospitals. Meta-analyses suggest that CBM-I has ***large effects on its target (Hedges's g = 0.81)***[37,48]. For studies delivering multiple sessions of CBM-I, ***effects on clinical symptoms are also large***. Most relevant to the current proposal, 10 studies support the ability of the WSAP CBM-I task to engage its target and improve clinical symptoms[40–42,56–61]. Of these, 7 double-blind RCTs yielded ***medium to large between-group effect sizes (d's = .48 to 1.05) for clinical symptoms that are comparable to existing evidence-based treatments.*** Of note, moderator analyses found that individuals with more biased cognition at baseline benefit more from CBM[62,63]. Thus, it is likely that effect sizes will be larger and more reliable in future studies that target this intervention to participants based on this dimension.

To date, the available data is limited primarily by small sample sizes, but are rigorous in design with double-blind randomized controlled trials comparing CBM-I to a placebo task. Additionally, few studies have tested the long-term effects of CBM-I. Preliminary evidence suggests that cognitive and symptom changes may endure for at least two weeks and up to six months[64–68]. The proposed study will provide crucial follow-up data to determine whether changes endure at 3 months post-discharge.

CBM-I is an ideal hospital augmentation because it is brief (i.e., 10-minute sessions), standardized to ensure reliable delivery, requires minimal staff time, requires minimal language skills and does not require patients to apply complex theories on their own. Combining CBM-I with hospital care and continuing following discharge is consistent with recent guidelines for on-line treatments recommending a standardized, concentrated dose followed by spaced out, booster sessions[69].

Pilot study in a partial hospital. Participants (*n* = 65) met criteria for a range of diagnoses, and 70% met criteria for moderate or high suicide risk on the clinician-administered MINI[75](specific suicide plans and suicidal gestures and attempts). The average number of prior hospitalizations was 2 (range 0 to 20). This pilot study did not include a measure of functional impairment; however, a prior sample from the same partial hospital reported significant disability on the Sheehan Disability Scale (*M* = 7 (out of 10) for each domain).

Does interpretation bias matter in a hospital population? Almost all prior studies of interpretation bias have compared a healthy control group to a psychopathology group; thus, we first examined the clinical relevance of interpretation bias *within* a SMI sample. Even in a restricted range of high symptom severity in our partial hospital, robust associations were found with interpretation bias. Controlling for baseline symptom severity, **patients who endorsed fewer benign interpretations at admission were less likely to respond to treatment** (defined as "very much improved" on the self-reported Clinical Global Improvement Scale), and this model **accounted for 28% of the variance in treatment response.** Interpretation bias upon admission also prospectively predicted **suicidal ideation at discharge** better than any other demographic or clinical variable[76].

Randomized Controlled Trial. Patients were randomly assigned to CBM-I or a neutral control condition. All individuals received treatment as usual at the partial hospital. Patients completed the 10-minute task each day they attended the partial hospital on a laptop computer. Assessments of interpretation bias and symptoms occurred upon admission and discharge.

Feasibility and acceptability: 99% of participants completed daily sessions of CBM-I. Attrition rate for the discharge assessment was low (11%), typically due to inpatient hospitalization or an

unexpected discharge. Patients easily fit the brief task into either their lunch break or between appointments. A bachelor's level clinic staff member delivered CBM-I in this pilot study. Thus, the CBT treatment providers were not directly involved. Not requiring a mental health clinician substantially improved the scalability of the intervention. An exit questionnaire revealed moderate to high satisfaction. On a scale of 1 to 7, patients' mean helpfulness rating was 5.2 (*SD*=1.3). Qualitative feedback revealed that most patients found the intervention relevant and a helpful complement to CBT. Patients noted an increased awareness of negative thought patterns, a flexible interpretation style, and interruption of their automatic associations. Patients connected CBM-I with the CBT they received even without the CBT therapist being involved: "*It helped me examine and challenge my Negative Automatic Thoughts"* – a term presented in the CBT groups and *"It helped solidify the program".*
Target engagement: Following an average of 7 sessions, CBM-I decreased negative interpretations (*d* =2.59) and increased benign interpretations (*d* =2.28) of ambiguous situations, both of which significantly differed from a neutral comparison condition. In the CBM-I group, **number of sessions correlated with change in negative interpretations** (*r* = .37, *p* =.03), providing preliminary evidence for a dose-response relationship.
Clinical outcomes: In patients who exhibited an interpretation bias upon admission (defined as endorsing ≥ 60% of negative interpretations), there was a significant treatment effect on the Clinical Global Improvement Scale: 36% of patients completing CBM-I were classified as responders ("very much improved") compared to 0% in the control, $\chi^2 = 4.41$, $p < .04$**.** There was also a moderate between group effect size for improvement in well-being (*d* = 0.6).

In sum, this pilot study revealed **good acceptability and feasibility**, **target engagement**, and preliminary evidence that CBM-I may augment partial hospital treatment effects on **global improvement and well-being**. However, this initial study did not include a comprehensive assessment of interpretation bias, nor any mid-point or follow-up assessments. Moreover, it only offered a basic, non-personalized, computer version of CBM-I during hospitalization (~7 sessions). Given the preliminary evidence for a dose-response relationship, the proposed study will allow patients to continue treatment following discharge from the hospital to consolidate and generalize changes in cognition once individuals return to their daily lives. The proposed study will follow patients 3-months after discharge to evaluate the durability of cognitive changes, and the link to primary (clinical global improvement; psychosocial functioning) and secondary outcomes (e.g., suicidal ideation, rehospitalization).

Rationale for Proposed Study.
Individuals who require a hospital level of care are at risk for relapse, rehospitalization, and suicide, particularly during the months post-discharge. Augmentation strategies that can be reliably delivered both in the hospital and continued during the transition to outpatient care are urgently needed. Interpretation bias, a crucial mechanism underling many forms of psychopathology, is not sufficiently altered for all individuals by existing treatments. CBM-I, a low-intensity intervention, engages interpretation bias and leads to symptom improvement. However, apart from our pilot study, CBM-I hospital delivery procedures have not been developed or tested. Thus, we propose to develop a smart-phone delivered intervention, *HabitWorks,* to allow better accessibility, patient engagement, assessment, and a means to bridge the transition from partial hospitalization to outpatient care. Results will provide pilot data to support an R01 effectiveness trial.

We will test HabitWorks as an augmentation to partial hospital (PH) treatment. Over 400 PHs in the US are used either as a step-down strategy or alternative to inpatient treatment. PHs provide intensive treatment during the day, allowing patients to return home in the evening. Results obtained from proposed study should generalize because the structure of the proposed

site is consistent with the structure of partial hospital and day programs across the US (e.g.,[70]). Acceptability data should also be relevant to individuals receiving inpatient hospitalization because half of patients attending the partial hospital are referred from inpatient care.

I. SPECIFIC AIMS

The primary goals of this R34 pilot effectiveness trial are to develop HabitWorks for partial hospital augmentation and transition to outpatient care and obtain pilot data to support a fully-powered R01 effectiveness trial.

Aim 1: Develop a smart-phone delivered intervention to augment hospital care
Aim 2: Obtain pilot data to support a fully-powered RCT, including measures of:
(a) Target engagement (improvement in interpretation bias)
(b) Feasibility and acceptability of HabitWorks and procedures for hospital and home delivery
(c) Clinical global improvement and functioning
We hypothesize that the HabitWorks intervention and research procedures will meet a priori goals for feasibility, acceptability, and clinical utility (see data analysis section).

Aim 3 : Obtain pilot data on CBM's effect on suicidal ideation and behaviors.

III. SUBJECT SELECTION

Phase 1: Development (COMPLETED)
In this first phase of this R34 pilot effectiveness trial, there will be no human subjects. The PI will meet with various stakeholders (e.g., clinicians at study site, clinic directors, BHP Patient Advisory Board) to obtain feedback about the HabitWorks app and research procedures.

Phase 2: Open Trial (Enrollment COMPLETE)
We will enroll 16 participants meeting the following inclusion criteria.

Inclusion criteria: a) currently receiving partial hospital care at the study site; b) age ≥18; c) at least moderate symptom severity (PHQ-9 or GAD-7 score ≥ 10); d) no current psychiatric symptoms that would prevent informed consent or understanding of research procedures (e.g., active symptoms of psychosis, mania), e) no current/active suicidal ideation (PHQ-9 item 9 > 1) and f) signing a release of information for treatment providers is an inclusionary requirement for study participation. Consistent with the RDoC, DSM-5 diagnosis will not affect eligibility. We anticipate a range of primary diagnoses, principally mood and anxiety disorders. Participants will be selected based on their baseline level of interpretation bias. Only patients who exhibit at least a minimal level of interpretation bias <80% accuracy on the WSAP) will be offered participation.

Source of subjects. The Behavioral Health Partial Hospital Program (BHP) at McLean Hospital admits over 850 individuals per year. The PI is Assistant Director of Research and a staff psychologist at the BHP, and Dr. Bjorgvinsson (Co-I) is Director. The BHP delivers group and individual CBT to patients with a range of psychiatric disorders, primarily mood, anxiety, personality, and psychotic disorders. Treatment focuses on concepts such as self-monitoring, cognitive restructuring, and behavioral activation. The average length of stay is 8 days. Patients are assigned a case manager, psychiatrist, and skills coach.

Recruitment methods. Study staff will review partial hospital patients' scores on the PHQ-9 and GAD-7 to determine initial eligibility. On patients' second day at the BHP, study staff will offer participation to those who score above the cut-offs. Interested patients will complete the interpretation bias assessment to determine eligibility. Patients may also express interest to study staff via flyers posted at the BHP.

Phase 3: Randomized controlled trial.

In this Randomized Control Trial, we will recruit 64 partial hospital patients. All inclusion and exclusion criteria, sources of subjects, and recruitment methods are the same as detailed in the Phase 2: Open Trial, except that current/active suicidal ideation criteria will be removed, such that individuals with all scores for phq9 item 9 are eligible. Further, after reaching our initial recruitment goal of 64, we will continue to recruit those participants that identify as BIPOC in order to achieve our proposed percentage of BIPOC participants.

III. SUBJECT ENROLLMENT

Procedures under existing BHP protocol:

Upon arrival to the Behavioral Health Partial Program, all patients will be oriented by the Community Residence Counselors and/or Nurse Practitioner (all CITI certified staff members) to the program, building and set-up of the treatment. Once oriented, patients will also be informed that as part of their treatment at the BHP they will be completing extensive self-report measures and a diagnostic interview. The Community Residence Counselors will explain to patients about our current research study examining the efficacy of CBT in naturalistic settings and ask whether or not they would like to consent to having their assessments be de-identified and included in our research database. It will also be explicitly instructed to patients, that if they were to refuse consent/participation, their treatment at the BHP will not be affected in any way. Patients will have the option to rescind their consent/participation at any point, and subsequently the Research Coordinator will take the appropriate measures to accommodate this decision. After obtaining informed consent from patients for the main effectiveness study, clinical staff will review a flyer about other studies being conducted in the program. Thus, clinical staff will inform patients of the research prior to staff approaching eligible participants. BHP clinical and research staff will reinforce that participation is voluntary and the decision not to participate will not affect their care at any time.

Procedures under proposed protocol:

The research coordinator or another member of the study staff will approach potentially eligible patients on their second day in the program and inform them about the study. During the Open Trial patients approached scored above a 9 on PHQ-9 or GAD-7, PHQ-9 item9 < 2 and they consented to main BHP study. During the RCT patients approached scored above a 9 on PHQ-9 or GAD-7 and had no criteria for PHQ-9 item 9 and can consent to main study at any time prior to consenting to the current study. Interested patients will then receive a detailed description of the study procedures, risk, and benefits and will review a study fact sheet for remote consent with trained study staff. They will then complete the interpretation bias assessment to determine eligibility to participate in the trial.

Randomization. We will use MINIMPY software to randomize participants to HabitWorks or Symptom Tracking. MinimPy is a desktop application program for sequential allocation of subjects to treatment groups in clinical trials by using the method of minimisation (https://sourceforge.net/p/minimpy/wiki/Home/).

We will enter age and baseline level of interpretation bias as variables for which the program will balance group assignment. The PI will randomize all participants following their eligibility session.

V. STUDY PROCEDURES

Phase 1: Development (COMPLETED)

The team will develop the HabitWorks smartphone app:
Harnessing the strength of smart-phone technology to enhance skill acquisition, HabitWorks will prompt patients to complete a practice session at set times to ensure adequate dosage and spacing of sessions. We will employ techniques known to enhance user engagement, such as progressing through levels, assigning points for correct responses, and tracking of progress. These reinforcing features may improve adherence, which may ultimately enhance effects on interpretation bias. We will develop the HabitWorks intervention to address common barriers to eventual implementation (e.g., customizability/personalization, ease of use)[88]. As part of a different project (MH097820), the PI developed an algorithm that creates a personalized CBM intervention for anxiety disorders based on demographic and clinical characteristics. We will develop a similar algorithm for a SMI population. Specifically, HabitWorks will use demographic questions, measures of symptom severity (see Measures), and questions about specific types of situations that are most relevant for the patient to create a personalized stimulus set (e.g., someone with financial worries will see trials related to this domain; a participant without children will not see stimuli related to parenting). We will create the stimulus pool from our previous trials, comprising a minimum of 600 word-sentence pairs. This large pool of stimuli will allow the intervention to present a mixture of new word-sentence pairs in each session.

We will work with the software programmer to create a user-friendly and visually appealing smart-phone app, as well as the back-end infrastructure to access and manage the data through Partners RedCap. The app will use SSL encryption, and no HIPAA-defined personally identifiable information will be collected via the app. The app will be developed through Apple's Research Kit and Android's ResearchStack, both of which are open source frameworks that allow researchers and developers to create apps for medical research.

Phase 2: Open Trial (Enrollment COMPLETE)

We will conduct an open trial to obtain pilot data. In the open trial, we will enroll 16 patients with assessments at pre-, post-, 1-month, and 3-month follow-ups to pilot the measures we expect to use in the RCT. At the end of the 1st iteration (*n*=4), the PI will compare actual data to target feasibility and acceptability outcomes. Deviations from target outcomes will prompt investigation and discussion with the research team and advisory board, and possible revision of the intervention or research procedures. We will repeat this process in 3 more iterations of 4 patients. The open trial will inform the design of the RCT.

This is a sub-study under the existing protocol entitled "Establishing the Effectiveness of Cognitive-Behavioral Partial Hospitalization for Anxiety, Depression, and Overall Functioning" (# 2010-P-001047/6). Data obtained under the existing BHP protocol will be shared with Investigators from this study.

Procedures under existing BHP protocol:
This research will be conducted with each patient who enters our program (up to 900 adult patients each year). As the Behavioral Health Partial Program is an adult CBT-based program, all patients are at least 18 years of age and up. Upon registration in our program, patients will receive the Mini-International Neuropsychiatric Interview (M.I.N.I.), a 20-45 minute non-invasive, structured diagnostic psychiatric interview to assess for psychiatric diagnostic criteria. Patients will also be asked to complete a self-report questionnaire assessing for demographic variables, symptom severity, functional impairment, and CBT skill acquisition upon registration, and upon

discharge. Information will be stored on-site, in a locked drawer, in a secure office. Patients' original questionnaires will be maintained for no longer than five years. Only the Principal Investigator (Courtney Beard), Research Coordinator, Nurse Director (Lynn Kopeski), and Program Director (Throstur Bjorgvinsson) will have access to PHI. However, the majority of PHI will be stored electronically. The proposed research will be using RedCap Database, an encrypted, electronic database that is both HIPPA compliant (Health Insurance Portability and Accountability Act) and approved by Partners IRB for the administration and storage of human subject information (for additional information on the RedCap Database feature see http://rc.partners.org). To minimize inconvenience and provide maximum benefit to patients, data collection will be streamlined as a part of standard clinical care. Clinically salient information, including diagnostic output and patient's self report scores, will be highlighted and presented to clinical team managers and others involved in patient services. Non-BHP patients will not be able to participate in this research.

Procedures for Proposed Protocol:
Participants' data collected as part of protocol (# 2010-P-001047/6) will be used to determine eligibility for this study, and to characterize the demographic and clinical characteristics of the sample and as outcome assessments. Thus, only participants who consent to the main BHP study protocol will be eligible for the current study.

On patients' second day at the BHP, staff will offer participation Interested patients will complete the eligibility assessment. Study staff will immediately review scores on the measure of interpretation bias (WSAP; see Measures) to determine eligibility. If eligible, they will complete the remaining pre-assessment measures. If ineligible, patients will be compensated and continue with treatment as usual at the BHP,

The partial hospital employs a bachelor's level progress monitoring coordinator who collects self-report data from patients and transmits this information to treatment teams. Identical to the pilot study, the PI will train this person to orient patients to HabitWorks and reinforce the rationale and instructions provided in the videos embedded within the app. The staff member will also conduct brief, in-person "check-ins" as often as desired by the patient, to answer questions about the intervention, provide accountability for the patient, and to provide encouragement. This extra support and human connection with the HabitWorks program should ensure adherence during the acute phase of treatment. On occasions when the progress monitoring coordinator is unavailable, a member of the study staff may provide the orientation and check-ins.

Participants will complete a task designed to improve interpretation biases. Each session includes 150 trials of the previously validated word-sentence association paradigm during each session (~10 min). The task presents ambiguous sentences ("You failed an exam") and provides positive feedback ("you are correct!") when participants endorse benign interpretations/attributions ("difficult test") and negative feedback ("you are incorrect!") for negative interpretations/attributions ("stupid").

Once enrolled, participants will complete HabitWorks daily on their smart phones in a quiet room while attending the partial hospital, three times per week at home for 1-month following discharge, and as desired during the final 2 months. Sessions during the follow-up period will include approximately 75 trials and thus will only require 5 minutes to complete.

During the 1-month post-acute period, participants will complete assessments of symptoms (PHQ-9 and GAD-7) as often as desired, including optional once weekly check-ins and daily assessment of affect (see EMA description in Measures). These surveys will be administered

via Metricwire. The Metricwire app was designed to protect participants' privacy, confidentiality, and data security. Only research personnel will have access to study information. Data collected by the Metricwire app is encrypted, and downloaded by the researcher to the local research server in a de-identified format (i.e., subject ID number). The local research server is only accessible by study staff. Study staff will provide orientation to the app and answer any questions regarding the assessments and data collected.

Treatment phase	***Location***	***Frequency of sessions***	***Session duration***
Acute *(1 to 14 days)*	*Hospital*	*Daily to augment CBT-based hospital treatment*	*10 min*
Transition *(1-month)*	*Home*	*3x per week to transition from intensive hospital to outpatient care*	*5 min*
Long-Term *(2 mo)*	*Home*	*Sessions completed as desired by individual*	*5 min*

Following Long-Term phase (post 3months from discharge) EPIC Research trained study staff will check every patients EMR, whether or not they completed the 3month assessment, for data on rehospitalization or ER visits and the reason why. This data will then be de-identified and kept in partners secure storage (Dropbox).

Retention. Post-discharge, staff will monitor participants' progress with the HabitWorks app daily and will call participants who have not completed any sessions in the past week. The purpose of these phone calls will be to help identify barriers and brainstorm potential solutions. To increase retention, we will: a) obtain contact information of individuals who will always know how to reach participants; b) pay participants for assessments; and c) provide transportation if needed, flexible scheduling for the assessments, and in rare individual cases conduct interviews via telephone.

Measures.
Participants will complete measures that are already administered as part of standard clinical care at the BHP.
The Mini International Neuropsychiatric Interview (MINI) is a structured interview assessing for DSM-V Axis I disorders. The MINI will be administered by doctoral practicum students and interns in clinical psychology who will receive weekly supervision by the post-doctoral fellow.
The PHQ-9 is a brief self-report questionnaire assessing symptoms of depression. Patients complete the PHQ-9 at daily.
The GAD-7 is a brief self-report questionnaire assessing symptoms of anxiety. Patients complete the GAD-7 daily.
The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q[97]) will assess satisfaction and quality of life.
To assess suicidal ideation and behaviors (lifetime, past month), we will use the interview administered *Columbia Suicide Severity Rating Scale* (CSSRS[98]). During remote assessments, when clinical interview is not possible, we will use an adapted form of the CSSRS as a self report measure.

Participants in proposed study will complete the following additional measures:

WSAP[23,41]. Word-sentence pairs representing benign or negative interpretations are presented, and patients decide if they are related or not. In the assessment version of this task, no feedback is given about the accuracy of participants' responses. The task will record reaction times for 4 WSAP trial types (endorse benign, reject benign, endorse negative, reject negative), reflecting the relative speed or ease with which participants make interpretations. We will

calculate reaction time bias scores for each trial type (negative vs. benign). The task will also record participants' responses (yes/no) for each trial type (negative vs. benign) to allow calculation of the percentage of negative and benign interpretations endorsed. In the case of remote recruitment in phase 2b and 3, the assessment version of the WSAP will be used as a screening tool prior to the Pre-treatment.

Schedule of Assessments	**Pre**	**Daily**	**Post**	**1-mo**	**3-mo**
Interviews					
MINI	X				
CGIS			X	X	X
WSAS	X		X	X	X
Longitudinal Interval Follow-Up Eval				X	X
Qualitative Exit Interview (open trial and first 20 in RCT)				X	
CSSRS	X			X	X
App or Computer Delivered					
***The HabitWorks app will deliver all daily surveys. Redcap will be used to deliver computerized surveys during in-person assessments.**					
Demog. Form, CEQ	X				
PHQ-9; GAD-7	X	X	X	X	X
Q-LES-Q, BHS, CFI, MPS, GSE	X		X	X	X
Exit Questionnaire				X	
WSAP	X	X	X	X	X
Scenario Recognition Task				X	
EMA PANAS	X	X	X	X	X
CSSRS- Self Report	X			X	X
System Usability Scale- HW condition				X	
TWEETS- HW condition				X	

The Scenario recognition task is the most widely used assessment of interpretation bias in CBM-I[91] and will ensure that effects are not solely attributable to practice or method effects. In brief, participants first read 10 ambiguous scenarios and a comprehension question to ensure they actually read the scenario. In the second phase, participants read the title of the ambiguous scenario followed by four versions of the final sentence presented in a random order. Sentences represent a) a possible positive interpretation, b) a possible negative interpretation, c) a positive foil, and d) a negative foil. Participants rate each sentence for its similarity in meaning to the original story using a 4-point scale ranging from 1 (very different in meaning) to 4 (very similar in meaning). We will calculate the average similarity rating for negative and positive interpretations.

Co-primary clinical outcomes will include stake-holder relevant measures of global improvement and functioning. The PI will train study staff to administer these brief scales and will monitor reliability using established procedures at the BHP.
Clinician-administered Clinical Global Improvement Scale (CGIS[93]) to assess global improvement.
Clinician-rated 5-item Work and Social Adjustment Scale (WSAS[94]) to assess interference caused by the patient's symptoms in the domains of work, home management, leisure, and family relationships.

Other self-report measures will include:

Credibility Expectancy Questionnaire[104] to assess patients' beliefs about the treatment expectancy (affectively based) and treatment rationale credibility (cognitively based).

Exit Questionnaire to assess patients' satisfaction with the treatment provided.

Beck Hopelessness Scale (BHS[99])) to assess negative attitudes about the future.

Cognitive Flexibility Inventory: The Cognitive Flexibility Inventory is a measure of mental flexibility and assesses the degree to which individuals are able replace maladaptive thoughts with adaptive ones and maintain a balanced mindset.

15-Item Multidimensional Perfectionism Scale (short form): The MPS is a widely used self-report measure of perfectionism.

10-item General Self Efficacy Scale: The GSE is a widely used self-report measure of self efficacy.

Ecological Momentary Assessment (EMA)
We will pilot the use of EMA to assess fluctuations in positive and negative affect using the PhenX Toolkit recommended measure PANAS-X [100]. During the 1-month transition phase, participants will complete the PANAS-X 4 times every day via the smartphone app. The surveys will be administered at random times during each one of 4 stratified blocks of time (9am-12pm, 12-3pm, 3-6pm, 6-9pm).

Other interview measures will include:
The Longitudinal Interval Follow-Up Evaluation (LIFE[103]*)* to assess psycho-pharmacotherapy use, including any medication or dosage changes.

Study staff will conduct a qualitative exit interview with prompts about overall patient experiences, acceptability and feasibility, relevance of the stimuli, and user-experience of the app.

Treatment adherence. Number of sessions completed will be recorded by the app and will be used as both a measure of feasibility/ acceptability, and as needed as a control variable in analyses.

Compensation. Participants will receive compensation for their time to complete assessments. Participants will receive $20 for the eligibility assessment and pretreatment assessment, and an additional $20 for the post-treatment assessments. They will receive $30 for the 1-month and 3-month follow-up assessments, $30 for completing at least 80% of the EMA surveys each week for 1 month, and $20 for the post-treatment qualitative interview (open trial only).

Phase 3: Randomized Controlled Trial
We will recruit 84 participants for the RCT with optional assessments at pre-, post-, 1-month and 3month timepoints. Follow-up assessments at the 1-month and 3-month timepoints will be considered optional for participants. In this RCT we will randomize individuals to receive the experimental condition HabitWorks or a Symptom Tracking condition. Those in the HabitWorks group will complete the CBM task via smartphone application as an augmentation to treatment as usual(TAU), while those in the Symptom Tracking Group will complete weekly symptom monitoring surveys as an augmentation to TAU.

Procedures under existing protocol:
All procedures under existing BHP protocol are remaining the same as the Open Trial, except for the changes in the inclusion criteria that eliminates the PHQ-9 item 9 score <2 requirement and restricts additional recruitment to BIPOC participants with the goal of reaching our proposed percentage of BIPOC participants.

Procedures for Proposed Protocol:
The research coordinator or another member of the study staff will approach potentially eligible patients (scoring above a 9 on PHQ-9 or GAD-7) on their second day in the program and inform them about the study, and send them a brief screening survey to assess initial eligibility prior to study consent and enrollment (i.e., owns an iPhone, willing to sign a release of information for outpatient providers, willing to use the app per protocol and willing to complete follow-up assessments). If patients are eligible based on this initial screening questionnaire, they will then receive a detailed description of the study procedures, risk, and benefits and will review a study fact sheet for remote consent with trained study staff. Additionally, those patients who did not originally consent to the BHP main study, will have to consent to the main study in order to be eligible for the RCT. They will then complete the interpretation bias assessment to determine eligibility to participate in the trial.

On patients' second day at the BHP, staff will offer participation. Interested patients will complete the eligibility assessment. Study staff will immediately review scores on the measure of interpretation bias (WSAP; see Measures) to determine eligibility. If eligible, they will complete the remaining pre-assessment measures. If ineligible, patients will be compensated and continue with treatment as usual at the BHP. After the eligibility session, patients will be randomized into either HabitWorks or Symptom Tracking groups by the PI.

The PI will train research staff to orient patients to HabitWorks and Symptom Tracking conditions and reinforce the rationale and instructions provided in instructional videos.

HabitWorks
Participants assigned to HabitWorks will complete the same procedures as outlined in the Open Trial. Specifically, participants will complete a task designed to improve interpretation biases. During each session, participants complete the previously validated word-sentence association paradigm (~10 min). The task presents ambiguous sentences ("You failed an exam") and provides positive feedback ("you are correct!") when participants endorse benign interpretations/attributions ("difficult test") and negative feedback ("you are incorrect!") for negative interpretations/attributions ("stupid"). Sessions during the transition phase are shorter (~5 min).

Once enrolled, participants will be asked to complete HabitWorks daily on their smart phones in a quiet room while attending the partial hospital, at least three times per week at home for 1-month following discharge, and as desired during the final 2 months. During the 1-month post-acute period, participants may complete assessments of symptoms (PHQ-9 and GAD-7) as often as desired, including optional once weekly check-ins for the study. For people in the HabitWorks condition, these surveys are administered via the HabitWorks app.

During the 1-month post-discharge period, participants will also complete daily assessment of affect (see EMA description in Measures). These surveys will be administered via Metricwire. The HabitWorks and Metricwire app was designed to protect participants' privacy, confidentiality, and data security. Only research personnel will have access to study information. Data collected by the Metricwire app is encrypted, and downloaded by the researcher to the local research server in a de-identified format (i.e., subject ID number). The local research server is only accessible by study staff. Study staff will provide orientation to the app and answer any questions regarding the assessments and data collected.

HabitWorks Treatment phase	***Location***	***Frequency of sessions***	***Duration***

***Acute** (1 to 14 days)*	*Hospital*	*Daily to augment CBT-based hospital treatment*	*10 min*
***Transition** (1-month)*	*Home*	*3x per week to transition from intensive hospital to outpatient care, 4x daily affect surveys, weekly symptom monitoring survey*	*15 min/day*
***Long-Term** (2 mo)*	*Home*	*Sessions completed as desired by individual*	*5 min*

Symptom Tracking
Participants assigned to the Symptom Tracking condition will be presented with a treatment rationale about the benefits of self-monitoring. They will complete daily symptoms surveys as part of routine clinical care while attending the BHP and will complete optional weekly symptom surveys, as well as the EMA, during the month post-discharge via the MetricWire app. Additionally during the Long Term phase, months 2 and 3 post discharge, participants can complete weekly symptom monitoring surveys as desired.

Symptom Tracking Treatment phase	***Location***	***Frequency of sessions***	***Duration***
***Acute** (1 to 14 days)*	*Hospital*	*No additional treatment, self-monitoring as part of TAU*	*na*
***Transition** (1-month)*	*Home*	*4x daily affect surveys as well as weekly symptom monitoring survey*	*15 min/day*
***Long-Term** (2 mo)*	*Home*	*Symptom monitoring surveys as desired*	*2min/week*

If under any circumstance in-person assessments are not possible, all study assessments and procedures can be completed remotely via telephone, encrypted email, or video-call, depending on the preference of the participant (see Risks and Discomforts section). Additionally, in cases of remote recruitment, participants will be screened over the phone and will be sent the assessment version of the WSAP (see measures) to assess eligibility prior to consent.

Retention. Post-discharge, staff will monitor participants' progress with the HabitWorks app and MetricWire app and will call participants who have not completed any sessions in either app over the past week. They will monitor this each week for the month of transition phase. The purpose of these phone calls will be to help identify barriers and brainstorm potential solutions. To increase retention, we will: a) obtain contact information of individuals who will always know how to reach participants; b) pay participants for assessments; and c) provide transportation if needed, flexible scheduling for the assessments, and in rare individual cases conduct interviews via telephone. In the event that a participant is unable to attend follow-up assessments, or follow-up assessments are not occurring in person, we will conduct the entire assessment through remote methods such as encrypted email, phone call, and video call. We will follow these procedures for both treatment conditions.

Measures:

All measures from the Open Trial will remain the same. Additionally, the RCT will include the following new measures:

Edinburgh Handedness Inventory- Short Form[116] is a 4-item widely used validated measure of handedness. The EHI will be used to determine eligibility for the EEG Assessment. Participants rate how often they use their left or right hand in 4 different practical examples on a scale of +100 ("Always Right") to -100 ("Always Left"). We will consider a score of +50 or above as right handed and eligible for EEG.

The System Usability Scale(SUS[117]): The SUS is a 10-item assessment of the usability of a given product or service, and was intended to be used for all types of technological interventions. It collects the subjective self-report of usability and specifically relates to user experience of effectiveness, efficiency, and satisfaction. Participants will rate their agreement on a 5point likert scale ranging from 1(Strongly Disagree) to 5(Strongly Agree). This survey will be administered at the 1-Month Assessment, only for individuals in the HabitWorks condition.

The Twente Engagement with Ehealth Technologies Scale (TWEETS[118]): The TWEETS is a 9-item self-report measure used to assess user engagement with health apps. It will be used to assess the level of cognitive, affective, and behavioral engagement that participants have with the HabitWorks app. Participants will rate their agreement on a 4point likert scale ranging from 0(strongly disagree) to 4(strongly agree). This survey will be administered at the 1-Month Assessment, only for individuals in the HabitWorks condition.

Study staff will conduct a qualitative exit interview for the first 20 participants regarding questions similar to the Open Trial, but pertinent to either Symptom Tracking or HabitWorks treatment conditions. Additionally participants will be asked about their experience in relation to the EMA in transition phase.

Finally, the Symptom Tracking condition will receive a different version of the Exit Questionnaire and the Credibility and Expectancy Questionnaire.

Compensation. Participants will receive compensation for their time to complete assessments. Participants will receive $20 for the pretreatment assessment, and an additional $20 for the post-treatment assessments. They will receive $30 for the 1-month and 3-month follow-up assessments, and $20 for the post-treatment qualitative interview (first 20 participants only). Participants will also be compensated for completing EMA surveys- they will receive $10 each week they complete any surveys at all, and a bonus $30 for every week they complete 70% surveys (19/28).

If, for whatever reason, a participant cannot or will not accept checks, the study will compensate with a one-time $50 giftcard.

VII. RISKS AND DISCOMFORTS

We believe that the risks of this study are minimal as most assessments used in this study are part and parcel of clinical care and are therefore no more invasive than treatment as usual in our program. The WSAP task and have been studied extensively by the PI and other researchers, with no adverse events reported.

Common Risks include: transient negative emotional reactions to the computer task, EMA protocol or questionnaires.

Uncommon Risks include: coercion, breach of confidentiality, and clinical deterioration,

All treatments carry with them the risk of loss of confidentiality, increased distress due to assessment or intervention procedures, and risk of ineffective intervention. Pharmacotherapy carries with it the risk of associated physical problems, including both mild and severe side

effects and interactions between medications. We note that pharmacotherapy is not proscribed for participants in this trial.

All patients will be receiving partial hospital care. Following discharge from the hospital, patients are expected to continue with their outpatient treatment plan.

Protection Against Risk. All aspects of the study will be conducted in accordance with HIPAA.

The areas of risk outlined above will be minimized by the following procedures.

1. The risk of potential coercion will be minimized by following standard procedures for obtaining informed consent. Study personnel will fully explain the study procedures, risks, benefits, and alternatives to all potential participants. It will be emphasized that their participation will have no impact on other services they receive at the partial hospital, or at other departments of McLean Hospital. Potential participants will not be recruited by their treatment team. All individuals will be reminded that there is no penalty for patients who choose not to participate or to withdraw from the study; they may refuse to participate or drop out of the study at any time without any negative repercussions from study staff, health care providers, or affiliated institutions. Consent will be documented through the individual's signature on the consent form. In the case of remote assessment, we will waive the documentation of consent, and verbal consent will be obtained through Zoom or telephone call. We will maintain e-copies of these remote consents, which will indicate who obtained consent and by which medium (telephone or Zoom), on our Partners Dropbox. During remote consent, we will provide participant with a copy of the consent form, which we will send via email. We will also include the following Partners required language in the summary sheet that provided to participants, regarding HIPAA: *We are required by the Health Insurance Portability and Accountability Act (HIPAA) to protect the privacy of health information obtained for research. This is an abbreviated notice, and does not describe all details of this requirement (see Partners Privacy Notice*). During this study, identifiable information about you or your health will be collected and shared with the researchers conducting the research. In general, under federal law, identifiable health information is private. However, there are exceptions to this rule. In some cases, others may see your identifiable health information for purposes of research oversight, quality control, public health and safety, or law enforcement. We share your health information only when we must, and we ask anyone who receives it from us to protect your privacy.* Dr. Beard has extensive experience supervising post-doctoral fellows and research assistants in conducting informed consent processes. The PI will be available in person or over the phone to answer any questions or provide additional information regarding the study. Additionally, in the case of remote recruitment, verbal consent for release of information will be obtained instead of physical signatures. Electronic copies of release of information forms, explicitly stating who obtained consent and how (ie. Verbally), will be stored on Partners approved Dropbox. Participants who decline participation or who do not meet inclusion/exclusion criteria will continue with treatment as usual at the partial hospital.

2. Potential risks due to loss of confidentiality will be minimized by having all information collected and handled by research staff trained to deal appropriately with sensitive clinical issues. All participants will be informed about the limits of confidentiality concerning suicidal intent, homicidal intent, suspected child abuse, and suspected elder abuse. Moreover, all information will be treated as confidential material and will be

available only to research and clinical staff. All self-report and interview data will be collected and stored in a Partners Hospital secure electronic database (using RedCap) which is stored on a secure server that is backed up on a daily basis. Cognitive bias data files will be available only to authorized personnel and no names or obvious identifying information will be stored in computer files containing study data. Patient identifying information will be stored in a separate database and will be password protected. Any paper files will be kept in a locked filing cabinet in a secured office. No subject will be identified in any report of the project. Further, when contacting participants during treatment or for post-treatment or follow-up assessments, no identifying information other than the name of the study staff member and the name of the site will be used when leaving messages or speaking to anyone other than the participant. Participants will be asked to provide informed written consent for audio-recording at the time of study entry (except for participants in Phase 2b). To assure the confidentiality and protection of participants with respect to audio recording, the following steps will be taken: a) audio -recordings will be labeled with the date and participant id number only; b) all recordings will be stored on a secure sever or in locked files in a secured office; c) access to the audio-recordings will be limited to individuals who will be rating the recordings for reliability and to the PI who will provide ongoing supervision; and d) all participants will have the right to revoke their consent for audio-recording or ask that any of the recordings be erased immediately or at any point during or after the study.

To assure the confidentiality and protection of data collected through the smart-phone application, no identifying information will be collected. The survey/ intervention application is being developed using ResearchKit(TM) for Apple devices and ResearchStack for Android—now the standard open source frameworks for deploying clinical research applications. The app will reside on patients' devices and only transmit data to the REDCap datastore. The survey app will transmit data to the REDCap datastore hosted by Partners. The app will only request data from the datastore in two circumstances: (1) to perform username/ password authentication, and (2) in the event that participant installs the app on a new or wiped phone, the app will retrieve responses to the customization portion of the intervention to personalize their instance of the app.

Some remote assessments may be conducted through Partners Enterprise licensed Zoom accounts assigned to each staff. This version of Zoom is configured to be HIPAA compliant. Staff will send password protected links to individual participants at the time of assessment. Zoom implements a range of encryption technology to ensure all content remains between the intended recipients. Video, audio and screen sharing are protected across platforms with a combination of asymmetric and symmetric encryption using AES-256 and AES-128. Recordings through zoom are at the hosts discretion and there are preventative measures in place to ensure there will be no unauthorized access to these recordings. Additionally we will only be storing the audio-recordings from these assessments, and these will be stored within Partners approved Dropbox.

As data are collected on the app, they are stored encrypted on the device until a connection is available for them to be pushed to the datastore using 128 bit SSL encryption, at which time the local copies are deleted. The app uses a unique ID assigned to the patient; no PII is generated or transmitted by the app. The Master Key (with subject ID and names) will only be accessible by research study staff, and located on our secure server. The server stores patient data using only the unique ID, no PII. The app requires a password for patient sign-in. All data obtained via the smartphone app is for research only and will not be placed in medical records or shared with clinical

staff.

Metricwire was designed to ensure data security, privacy, and confidentiality. Data are encrypted on the phones and uploaded to a secure server (using HIPAA compliant software which has been reviewed and approved by Partners RISO in multiple other projects) and downloaded by the researcher to the local research server in a de-identified format. All subject names will be coded. The master key (linking deidentified IDs to identifying information) will be stored securely on the Partners network and will only be accessible to study staff. No identifiable data will be stored on mobile devices.

3. We also plan to make the de-identified data from this study available via the NIMH Data Archive (NDA) accordance with NIMH policy, to be stored in the National Database of Clinical Trials (excluding Phase 2b).

4. The risks of possible distress due to the assessment and treatment procedures will be minimized by: a) using assessments and procedures which have been widely used in previous clinical and research studies; b) conducting assessments at the clinic that the participant attends (and is familiar with); c) reminding all individuals that they do not have to answer assessment questions that they find too distressing, and that they can discontinue participation at anytime; and d) having licensed clinical psychologists (Drs. Beard, Björgvinsson, or McHugh) on call during all assessments, sessions, and daily throughout the course of the study to counsel participants and help facilitate the stabilization processes for participants who report experiencing distress. Patients who complete sessions at home will be given phone numbers of the PI and study staff, as well as hours that each individual may be reached via telephone. They will be instructed to call should they experience any distress while completing the smart phone app. It is also possible that participants may become distressed should they experience technical difficulties at home. Prior to any home sessions, participants will have already completed daily sessions and will be fully competent to self-administer the program before attempting to complete at home. They will be instructed to call study staff should they experience any trouble with the program during regular work hours, and we will work with the patient to solve the problem. If they are accessing the program during non-working hours, they will be instructed to leave a voicemail for study staff, who will return their call as soon as possible the next business day. Of note, in previous CBM protocols delivered at home, patients did not report experience any distress completing the computer programs.

5. Minimization of risk of ineffective intervention

   The overall risk of possible ineffective intervention will be minimized by: 1) frequent monitoring (daily for all study participants); 2) allowing study participants to receive standard partial hospital level of care or outpatient care, including pharmacotherapy and psychotherapy; 3) reminding all participants at each contact of the emergency numbers they should call if they experience a significant worsening of symptoms and/or suicidal ideation; and 4) the study protocol specifying that, in the event of clinical deterioration of anxiety or depression symptoms, or increased suicidality, study subjects will be evaluated by a licensed clinician.

   To minimize risk of clinical deterioration of anxiety and/or depression, a protocol for close clinical monitoring has been established.

See SOP. In brief, we will not be monitoring symptoms and suicide risk via app surveys AT ALL throughout the study. Patients will be reminded multiple ways that they should not use study surveys as a means to communicate a need for clinical attention (see Lab SOP). If they are in distress they may reach out to outpatient providers or emergency services. As part of TAU, patients will create a safety plan with their providers at the time of discharge from the program and research staff will go over this plan with them, as another reminder of what to do in cases of emergency, as we are not following them. Upon discharge from the BHP, we will also be providing participants with a contact list for local crisis services throughout the state, and helping participants identify a few resources they could use. Participants will be reminded before each survey that they may skip the survey or stop the survey at any time, and that they should reach out to outpatient providers, suicide crisis numbers, or 911 in case of emergencies.

VIII. POTENTIAL BENEFITS

Potential benefits to all participants include a detailed psychiatric evaluation and increased assessment and monitoring of their anxiety and depression symptoms. If a participant's anxiety or depression worsens substantially, we will provide feedback to the partial hospital treatment team (acute phase). If the participant is at risk for a suicide attempt, we will take immediate action to safeguard that patient. All participants may also benefit from the opportunity to practice self-assessment skills (i.e., symptom tracking). We believe that serious risks (e.g., loss of confidentiality or major psychological distress due to study participation) to subjects are very unlikely. We have attempted to minimize these risks (as described above). While some risks may be more likely to occur (e.g., minor, transient psychological distress), these risks are much less serious. Therefore, the potential benefits of the proposed study seem to outweigh the potential risks of this study for the individual participants.

The overall goal of this research project is to learn more about the development of efficacious and easily disseminated treatments for SMI, thus, indirectly, all participants may eventually benefit from furthering science in this field, as may other individuals who suffer from these disorders.

Importance of the Knowledge to be Gained.

The results of this study will provide important information about the feasibility and acceptability of HabitWorks as a personalized, augmentation intervention for SMI. Approximately 4.1% of the adult US population suffers from SMI, defined as a mental disorder associated with significant functional impairment. In addition to serious functional impairment, individuals with SMI die 10-32 years prematurely, and are almost 13 times more likely to die by suicide. Hospitalization is common among those with SMI, and individuals requiring a hospital level of care are often treatment refractory and may benefit from the addition of a targeted augmentation strategy. Augmentation treatments that can be reliably delivered both in the hospital and during the transition to outpatient care are urgently needed.

The knowledge gained concerning the modification of pathological information processing in SMI will advance our understanding of mechanisms underlying psychopathology. This line of research will also add to the growing evidence for smart-phone delivered interventions as

potentially cost-effective and easily disseminated interventions. We believe that serious risks (e.g. loss of confidentiality or major psychological distress due to study participation) to subjects are very unlikely. While some risks may be more likely to occur (e.g. minor, transient psychological distress), these are much less serious. Thus, in relation to the importance of the knowledge to be gained, the minimal risk to participants is reasonable.

IX. MONITORING AND QUALITY ASSURANCE

Oversight of the participants' safety will be conducted by the PI and by a Data Safety and Monitoring Board (DSMB) comprising Efrat Shavit, M.D., Eliza Menninger, M.D., and Marisa Silveri, PhD. Dr. Shavit is a psychiatrist at the BHP (study site). She has experience treating individuals with SMI, managing their safety, and training residents in these areas. Dr. Menninger is Medical Director of the BHP and has decades of experience managing suicide risk in acute treatment settings. Finally, Dr. Silveri is a Neuroscientist and Director of the Neurodevelopmental Laboratory on Addictions and Mental Health at McLean Hospital. Her NIH-funded research examines cognitive ability and clinical indicators of mood, anxiety, and impulsivity, across healthy adolescent, emerging adult, and adult cohorts, and those with addictions and co-occurring psychiatric illnesses. Please see attached DSMB Charter.

Efficacy plan.

To ensure that valid, reliable, and accurate data are collected, we will audio-record all assessment interviews with the patient's permission. Self-report data will be obtained directly from the computer and stored in the secure database. Data collected from interviews will be entered into a secure database. All data will be reviewed and entered into the computer database a second time. Files from the two data entries will be compared in order to check for accuracy of data entry. Dr. Beard has extensive experience training research assistants and post-doctoral fellows in diagnostic and symptomatic assessments. Training involves a multi-stage process in which study staff: 1) meet regularly with Dr. Beard to obtain education about DSM criteria for the disorders being assessed and general interviewing techniques; 2) view training videotapes on the MINI, CGI, and other assessments being utilized; 3) attend a half to full day meeting in which the administration of the interview measures are reviewed in detail and role-plays are conducted; 4) view a skilled interviewer conducting two or more interviews with actual participants (with consent of these participants) and conduct interviews with actual participants while Dr. Beard is present; 5) are scored by Dr. Beard on aspects of their skill in completing the assessments and are deemed fully trained to conduct interviews independently, after achieving a passing score. Ongoing checks of assessment technique are conducted in a process to assure calibration and prevent rater drift, while also obtaining inter-rater reliability data. Assessment staff and research assistants regularly independently listen to and rate a MINI assessment. This provides inter-rater reliability data. After each staff member rates a given interview, we discuss ratings as a group, a process that ensures calibration with an expert diagnosis, and helps to prevent rater drift.

Safety Plan.

See Lab SOP attached.

The DSMB will review rates of adverse events to determine any changes in participant risk. A brief report will be generated quarterly for the study record and forwarded to the DSMB and annually to the Partners Healthcare Institutional Review Board. The DSMB members will be available to meet outside of the quarterly meetings, if necessary, to discuss concerns regarding a particular participant or research problem. If necessary, they will make appropriate recommendations for changes in protocol. The PI will meet weekly with study staff to review experiences with participants. All adverse events will be reported to the IRB per PHRC

guidelines: https://partnershealthcare-public.sharepoint.com/ClinicalResearch /Reporting_Unanticipated_Problems_including_Adverse_Events.pdf. The DSMB will inform NIH of any significant action taken as a result of DSMB findings. This study will use the NIH's Common Adverse Events (AEs) and Serious Adverse Events (SAEs) definitions for clinical research. Adverse events are defined as any event or outcome that has resulted in harm to the participant, has affected the participant detrimentally, has worsened as a result of participation in the study, or that has resulted in increased risk to the participant or others whether or not the risk actually results in harm.

In the event that a participant either withdraws from the study or the investigator decides to discontinue a client due to SAE, the participant will be monitored by the PI via ongoing status assessment until 1) a resolution is reached i.e., the problem requiring hospitalization has resolved or stabilized with no further changes expected; 2) the SAE is determined to be clearly unrelated to the study intervention; or 3) the SAE results in death. Unexpected events are defined as any event or outcome that was not described as a risk of participation in the research, or though described as a risk, the event or outcome has occurred with unexpected severity or frequency.

Lab Clinical Deterioration and Suicidality
Standard Operating Procedure (SOP)
Version date: January 20th, 2021

Procedures during partial hospitalization (while patient attends BHP)

All participants in this study will be receiving intensive partial hospital treatment during the acute phase of the study. Therefore, deterioration or suicide risk during this phase will be reported to the patient's clinical team manager at the BHP. At that point, the treatment team will manage the safety of the patient and determine whether inpatient hospitalization is required.

We will maintain regular communication with the patients' treatment team throughout the course of their partial hospital stay. Dr. Beard's office is in the same hallway as all of the BHP clinical team managers and psychiatrists. We will use the BHP's confidential voicemail system for non-urgent information and pagers for urgent clinical information.

Clinical Deterioration

As part of standard clinical care, the BHP's Progress Monitoring Coordinator (PMC) will monitor depression symptoms daily, via use of the PHQ-9 using RedCap. As part of standard clinical care, the PMC will notify the clinical team manager of any patient who experiences an increase of 5 or more points on the PHQ-9 from the baseline assessment. At that point, the treatment team will manage the safety of the patient and determine whether inpatient hospitalization is required. Each time the PHQ-9 total score increases by 5 or more points, the PMC will again notify the clinical team manager of the symptom increase.

Suicidality

As part of standard clinical care, the PMC will monitor suicidal ideation daily, via use of item 9 on the PHQ-9 using RedCap. As part of standard clinical care, the PMC will notify the clinical team manager of any patient whose experiences an increase from the baseline assessment (e.g., from a 0 to 1, from a 1 to 2, etc.). At that point, the treatment team will manage the safety of the patient and determine whether inpatient hospitalization is required. Each time item 9 on the PHQ-9 increases by one or more points, the PMC will again notify the clinical team manager of the symptom increase.

As part of standard clinical care, patients complete the Columbia Suicide Severity Rating Scale upon admission to the BHP. As part of this study, they will also complete it at post-BHP treatment. Answers of "Yes" to questions 4 or 5 on C-SSRS will result in emergent evaluation by licensed clinician (either BHP clinical team manager or Dr. Beard). During periods where the BHP is operating remotely, participants will complete the self-report version of the C-SSRS during study assessments. In these instances, study staff will monitor their responses in real-time, and will ensure that a licensed clinician is available at time of study assessment for emergent evaluation if necessary (Answers of "Yes" to questions 4 or 5).

Procedures following partial hospitalization (post-discharge from BHP)

At discharge as part of treatment as usual participants will create a safety aftercare plan with their BHP provider, and this plan will be gone over in their discharge session with research staff. In addition, staff will provide participants with a list of local crisis resources across the state, and ask participants to identify a few they could contact if needed. In this session we will reiterate that the research team will not be checking patients Weekly Check-Ins (PHQ/GAD) or the EMA surveys. Following discharge from the hospital, patients are expected to follow their aftercare plan with outpatient providers. During this time study staff will not be monitoring safety of any Mood Check ins completed by participants, nor will they be following the daily EMA surveys.

The smart phone app will clearly remind patients as they complete these forms each day that study staff will not see the data and thus, if they feel that they need attention, they should call their outpatient

providers, call 911, use the crisis text hotline, or go to their local Emergency Department. Additionally, if a patient indicates any level of suicidal ideation on the PHQ-9 (item 9 score ≥ 1), the app will generate a message urging the patient to call their outpatient providers, contact emergency services, or utilize the crisis text line if they are feeling unsafe. Additionally, the list of crisis resources provided to patients upon discharge will be available to view in the app FAQs.

Additionally, any symptom monitoring surveys completed in the Long Term phase will not be monitored at all by staff.

Suicidality

As part of this study, participants will complete the Columbia Suicide Severity Rating Scale at 1 and 3-month follow-up assessments. Answers of "Yes" to questions 4 or 5 on C-SSRS will result in emergent evaluation by licensed clinician member of study staff (Dr. Beard) for appropriate assessment and triage (see risk assessment section below). In addition to clinical interview, as well as when clinical interview cannot be scheduled, participants will complete a self-report version of the C-SSRS. When this occurs, study staff will monitor their responses in real-time, and will ensure that a licensed clinician is available remotely at time of study assessment for emergent evaluation if necessary (Answers of “Yes” to questions 4 or 5). If Dr. Beard is unavailable to conduct a risk assessment another pre-determined licensed clinical psychologist will reach evaluate the patient. If multiple risk assessments are required for the same participant, we will attempt to have the same clinician speak with the patient at all risk assessment timepoints

Risk Assessment

Risk assessments for suicidality (*CSSRS)* will be conducted by the close of business on the same day the notification was received. If the study participant has experienced significant deterioration but is not in immediate danger of hurting him or herself, we may take the following actions. First, we will inform the patient about procedures for contacting emergency services should they find themselves at risk for self-harm. Second, we will urge the patient to make an appointment with their outpatient provider as well. Third, with the patient’s consent, we will speak with one of their family members so that he/she can be aware of the seriousness of the patient’s symptoms and the agreed-upon treatment plan. Fourth, if the patient wishes additional treatment referrals or other referrals, we will facilitate these referrals.
Dr. Beard will conduct a suicide risk assessment to determine whether it is necessary to take immediate action to prevent the participant from causing harm to themselves. If Dr. Beard is unavailable to conduct a risk assessment another pre-determined licensed clinical psychologist will reach evaluate the patient. If multiple risk assessments are required for the same participant, we will attempt to have the same clinician speak with the patient at all risk assessment timepoints. If needed, actions that Dr. Beard may take include having a family member bring the person to McLean Hospital or sending an ambulance so that the individual may be evaluated for inpatient psychiatric admission.

Documentation

Study staff will document each time a participant is identified for clinical deterioration or suicidality. Documentation will include the following:

- Date of identification
- Reason for identification (e.g., increase on GAD-7)
- Date and time clinician contacted
- Outcome

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