Study Protocol and

Statistical Analysis Plan (SAP)

DEVELOPMENT AND PRELIMINARY TESTING OF A NON-REGULATED DIGITAL SERVICE THAT SUPPORTS COGNITIVE BEHAVIORAL THERAPY FOR DEPRESSIVE SYMPTOMS UNDER CLINICAL SUPERVISION

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Ethical approval:	**Mass General Brigham Institutional Review Boards (protocol # 2020P001958, approved on 04/08/2021)**
ClinicalTrials.gov identifier:	**NCT05386329**
Funding:	**This study was funded by Koa Health (formerly Telefonica Alpha). Investigators from MGH developed the Mindset app in collaboration with technologists and designers from Koa Health via a user-centered, iterative design approach. The investigators from MGH were responsible for the study design and for the execution of the study; authors from Koa Health supported the technical activities related to the development and deployment of the app, and provided funding for the project. Koa Health had no role in the recruitment of participants and had no access to data during the trial.**
Document Date:	**November 14, 2023 (shortened version)** **Last IRB-approved update: 09/19/23**

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Version	**Draft 1.0**

PRELIMINARY TESTING OF COMBINED DIGITAL COGNITIVE BEHAVIORAL THERAPY PLUS VIRTUAL TREATMENT FOR DEPRESSIVE SYMPTOMS

I. SPECIFIC AIMS

The overarching purpose of this project is to conduct an open trial to test the efficacy of digital CBT for when combined with virtual visits with a CBT therapist. Specifically, we seek to evaluate how digital CBT plus virtual treatment initially performs when deployed in a clinical setting to support treatment. This treatment will include the mobile CBT for depression app in combination with eight virtual visits delivered by doctoral-level psychologists or psychology interns with their master's degree over a period of 8 weeks. The therapist will be assigned once eligibility is determined and will offer 8 virtual treatment sessions in total in addition to unlimited access to the app. All virtual sessions will be no longer than 16-25 min. The combined CBT app plus virtual treatment will be tested in 28 patients.

Aim 1: Test feasibility and acceptability of the combined digital CBT plus virtual treatment. Examine uptake, patient satisfaction, clinician usability and satisfaction, sustained engagement, drop-out rates.

> Hypothesis 1a: We hypothesize that digital CBT plus virtual treatment will be feasible (based on uptake, engagement and drop-out rates).
>
> Hypothesis 1b: We hypothesize that digital CBT plus virtual treatment will be deemed acceptable both to patients and clinicians (based on descriptive statistics of patient satisfaction, app use, app feedback, clinician ratings (CGI Ratings) as well as qualitative feedback).

Aim 2: Examine preliminary efficacy of digital CBT plus virtual treatment for primary outcomes (i.e., reduction in severity of depressive symptoms) and secondary outcomes (e.g., quality of life at post-treatment, social and occupational functioning at post-treatment).

> Hypothesis 2a: We hypothesize that participants receiving digital CBT plus virtual treatment will evidence statistically significant reductions in HAM-D scores from baseline to post-treatment (week 8).
>
> Hypothesis 2b: We hypothesize that participants receiving digital CBT plus virtual treatment will evidence statistically significant improvement on secondary clinical outcome measures (i.e., functional impairment (WSAS) and quality of life (Q-LES-Q)) from baseline to post-treatment (week 8).

II. SUBJECT SELECTION

Overview:

To meet our target of 28 eligible participants, we expect to screen up to about 84 individuals. Detailed eligibility criteria are below.

A. Inclusion/Exclusion Criteria:

1. Inclusion criteria
    a. Adults (at least 18 years of age)
    b. Living in Massachusetts
    c. Current diagnosis of primary DSM-5 MDD, based on MINI
    d. PHQ-9 score ≥ 10, indicating the presence of at least moderately severe depressive symptoms
2. Exclusion criteria
    a. Psychotropic medication changes within 2 months prior to enrollment. Participants taking psychotropic medication must have been on a stable dose for at least 2 months prior to enrollment and not change medication during study period
    b. Past participation in ≥ 4 sessions of CBT for depression
    c. Current severe substance use disorder
    d. Lifetime bipolar disorder or psychosis
    e. Acute, active suicidal ideation as indicated by clinical judgment and/or a score ≥2 on the suicidal ideation subscale of the C-SSRS.
    f. Concurrent psychological treatment
    g. Does not own a supported mobile Smartphone with a data plan
    h. Lack of technology literacy that would interfere with ability to engage with smartphone treatment

B. Source of Subjects and Recruitment Methods:

We plan to enroll 28 participants. Potential participants may be informed about the study through MBTA advertisements, radio advertisements, MGB / Partners clinicians and research colleagues nationally, fliers posted in specialty clinics and hospitals, coffee shops, restaurants, laundromats, barber shops, churches, daycares, libraries, newspapers, universities, other public locations, through our program's website and a recruitment website we will create for this study, Partners Clinical Trials (Rally), listservs (e.g., MGH Broadcast), via social media (e.g., Facebook/Instagram ads, our program's Twitter account) on the Internet, and in online support groups. Individuals will also be recruited as part of our clinic's general recruitment protocol. Interested individuals will be referred to the study RA, who will provide more information about the research study and assess preliminary eligibility over the telephone. We will also use a screening questionnaire hosted on REDCap. The link to access this screener will be embedded within our recruitment website. This will help identify individuals who are likely to be eligible for the study.

III. SUBJECT ENROLLMENT

A. Method of enrollment, including procedures for patient registration and/or randomization

<u>Overview</u>

Potential participants will be preliminarily screened by a trained study staff member (e.g., RA) over the phone to establish their likely eligibility. We only ask for the potential participant's name and contact information at the end of the phone screen if the individual is eligible and interested in participating. The participants' contact information may also be gathered through the screening questionnaire on our recruitment website. Additionally, during the phone screen the RA may ask permission to send eligible and interested participants a Partners/MGH Authorization for Release of Protected or Privileged Health Information form, which participants may complete with their psychiatrist's or other healthcare provider's contact information and then send directly to the study RA. If permission is obtained, the study clinician may then contact the participant's healthcare provider to verify issues surrounding potential eligibility (e.g., if there is any question/concern about the anticipated stability of the participant's medications), based on information collected by the RA during the phone screen. Screening information of individuals who do not meet study criteria will be destroyed. Subjects will be enrolled by MGH. Potential participants will be given as much time as they need to consider participation, prior to providing informed consent. If suicidality is expressed to an RA during the phone screen, the RA will notify a licensed clinician member of the study staff immediately. Per our internal procedures, RAs will keep the suicidal individual on the phone until a licensed clinician member of the study staff arrives to conduct a telephone evaluation. RAs may contact a licensed clinician member of the study staff directly via e-mail during the phone call, and/or email other research assistants who can then alert a licensed clinician member of the study staff to promptly conduct an evaluation over the telephone.

Interested and eligible participants will be invited to complete the baseline assessment with the independent evaluator (IE) by secure, HIPAA-compliant video calling program (Zoom or phone). At that time, patients will be informed about the study's purpose and procedures and advised about alternative treatment options. Before eligibility is assessed, the IE, Dr. Greenberg, Dr. Bernstein, or Dr. Wilhelm will obtain electronic informed consent. The informed consent document will be provided to the potential participant electronically through REDCap, a secure data capture system, and they will be asked to select an "I agree" button and provide their signature in REDCap to indicate their consent (see more REDCap information below: "Monitoring and Quality Assurance"). The participant will be informed that they may download and save a copy of the consent form for their records. Self-report measures for the baseline assessment will be completed through a secure REDCap link emailed to participants if participants consent and are deemed eligible.

C. Procedures for obtaining informed consent (including timing of consent process)

Before participating in the screening and baseline assessment, patients will be given information about the study via phone and initial eligibility will be assessed. After this initial phone call, the RA will email interested potential participants a pdf copy of the informed consent document for review, prior to the screening/baseline assessment. Online consent will be used as recruitment is state-wide, prohibiting in-person written consent. The potential participants will be asked to abstain from signing the consent form until study procedures are discussed with the IE, or Drs. Wilhelm, Bernstein, or Greenberg, during the baseline screening video call. In cases where Zoom is used, before the baseline assessment appointments, the RA will send participants an appointment confirmation e-mail with detailed instructions for logging onto the HIPAA-

compliant Zoom software on their devices, which is used for video call assessments. In advance of the appointments, the RA may conduct a brief test call with the subject to ensure that the subject installed the software and can access it from their devices. For safety, the RA will collect an emergency contact from the participant, so that the IE will have this information on hand during the virtual baseline assessment. The emergency contact information will also be collected in the demographics form after the baseline interview with the IE for confirmation. At the start of the screening/baseline assessment, before beginning study procedures, the IE, or Drs. Wilhelm, Bernstein, or Greenberg will inform potential participants about the study's purpose and procedures and advise about alternative treatment options. If the individual wishes to participate in the study, the IE or Drs. Wilhelm, Greenberg, or Bernstein will obtain informed consent electronically by asking participants to click an "I agree" button and electronically sign the electronic informed consent document sent through REDCap, a secure data capture system. The person obtaining informed consent will also verify the participants identity by requesting to view a form of identification (e.g., government-issued driver's license). Participants will have the ability to download and print the electronic informed consent document, or save the pdf copy to their computer for their records. The research assistant will send participants a signed pdf copy of the consent form for their records.

D. Treatment assignment and randomization (if applicable)

N/A for the current study. All participants will receive the same treatment.

STUDY PROCEDURES

Email Correspondence

All email communications with participants will be sent in accordance with Partners' Send Secure email encryption policy.

A. Study visits and parameters to be measured

Phone screen: See section IV, "Subject Enrollment," above.

Screening/Assessment Calls and Procedures: The screening visit will take place over the phone (or HIPAA-compliant video conference call) and will last approximately 2-3 hours (with up to an additional hour on the computer for self-report assessments). Subjects will provide electronic informed consent with study staff (e.g., the IE; See Section C, "Procedures for obtaining informed consent" for further details). They will then be assessed by the IE for eligibility, using the below assessment instruments (see Table 1). Participants will complete self-report questionnaires online via REDCap. After the Baseline visit, participants will be notified by study staff (see appendix) regarding their eligibility status, and they will be given the opportunity to discuss this further with our study staff by phone. Reasons for ineligibility will be documented, and ineligible participants will also be provided with treatment referrals and resources. Eligible subjects will be taught to download the app and will receive a brief tutorial in using the app-based treatment. All participants will receive instruction in downloading the Koa Health Habits app as well. Please see the schedule of assessments and measures administered at each time point in Table 1. These assessments will require approximately 1 hour. These

assessment lengths are similar to those used in other studies in our program and have been well-tolerated by participants. To avoid dropout, participants will be paid $25 for mid-treatment, end-of-treatment, and 3-month follow up assessments.

Downloading the app(s): The IE or RA will assist participants in downloading the app(s) on their smartphone. The IE or RA will generate an enrollment code(s) for each study participant linked to their unique study identifier on the study server. Participants will download the study app(s) from the Apple iOS or Google Play stores. When subjects launch the study app(s) for the first time they will be prompted for the enrollment code. Study content will only be available to participants after entering their enrollment code. In this way, the app(s) cannot be accessed by individuals who have not been enrolled in our trial and given an enrollment code.

Passively Collected Data to be Measured: Data from sensors in participants' mobile phones may also be collected through the Mindset and/or Habits apps, to optimize the program through personalization and improvement of the app. Participants will not be required to use the Habits app and may opt out of this component. In order for Habits to continue to run in the background of participants' iPhones across the study period, participants must occasionally interact with the app once every 7 days, unless location is activated. For Android users, the participants do not need to access Habits apart from the first time for data collection to occur.

Treatment Format: Participants will complete app-delivered treatment on their personal smartphones, over the course of approximately 8 weeks (see "The Treatment" section below for an outline of the modules that the app includes). Forde et al. (2005) report that 6-8 therapy sessions is the optimal number of sessions for treating mild to moderate depression. Each treatment component will be presented through modules on the mobile app, and exercises will be logged and practiced through the app on one's smartphone. An advantage of app-based CBT for MDD is that participants can self-direct the frequency and duration of modules, and they can re-visit modules as many times as is useful to them.

Additionally, upon initiating the digital CBT treatment, each participant will be assigned a therapist with training in CBT and familiarity with MDD; all therapists will be supervised weekly by a licensed psychologist (see "Therapist Training and Qualifications," below). Participants will meet virtually with this therapist for a total of 8 treatment sessions to supplement and help guide them through the CBT app for MDD. All visits will be no longer than 16-25 minutes. During these sessions, the therapist will help the participants set treatment goals, evaluate and enhance motivation, answer questions about skills introduced via digital CBT, brainstorm ideas for between-session homework, and problem-solve should treatment barriers arise. In addition to sessions, participants can communicate with their therapist through a secure messaging system incorporated into the app throughout the 8-week treatment. The therapist will have a separate portal through the Mindset server to receive and respond to these in-app communications from patients. Patients will be notified that the therapist will respond to all in-app communications within 36 hours on weekdays. During the follow-up phase of the study (i.e., after week 8), participants will continue to have access to the app, but without the therapist support or messaging system.

Therapist Training and Qualifications: Doctoral-level clinicians (or pre-doctoral interns with master's degrees) will serve as therapists. All study therapists will be trained in the study protocol and participate in weekly supervision with a licensed psychologist. Previous findings from our BDD pilot trial (#2017P000293) in which only a BA-level "coach" was available to participants in addition to the CBT treatment app, suggest that even a light-touch focused on motivation and problem-solving is helpful in supporting treatment, with the app itself serving as the primary mode of treatment delivery. As such, though the therapists in this trial will have more training in CBT and will spend more time speaking one-on-one with participants compared to our previous trials, the current trial is still structured with the intention of having the CBT app serve as the primary treatment modality. Therapists will receive training prior to starting the trial (e.g., completing relevant MGH Psychiatry Academy CBT training course(s), and will be required to pass (>90% correct) the corresponding MGH Psychiatry Academy knowledge test to demonstrate proficiency). To ensure ongoing high-quality treatment, Dr. Wilhelm, or another study staff member who is a licensed clinician with expertise in CBT for MDD and related conditions will provide weekly supervision to therapists, with additional supervision as needed if questions arise. Further, sessions will be audio recorded for review, as 15% of randomly selected audiotaped sessions will be rated for competency and treatment adherence, similar to other NIH studies we have conducted.

The Treatment:
The CBT app includes the following components of CBT for MDD, which the therapist will also follow in virtual sessions: 1) education about a CBT model of MDD; 2) cognitive techniques to identify and challenge distorted thoughts related to one's MDD; 3) enhancing values (e.g., behavioral activation); 4) mindfulness (to help patients to learn to balance distressing emotional states with rational thinking and to control their attentional processes); 5) deeper level (core) beliefs; and 6) relapse prevention (to teach patients to expect and react effectively to setbacks that may occur during times of stress). Additionally, passively collected sensor data (described above) will provide information on changes in participants' mobility and sleep patterns. Our hope is that, in a future stage, the treatment could be adapted to address changes in sleep and mobility patterns (e.g., prompting the participant via a message through the app encouraging him or her to engage in the treatment when mobility is notably low).

Measures Descriptions

Diagnostic Measures

Mini International Neuropsychiatric Interview (M.I.N.I.) (Appendix)*:* The M.I.N.I. (Sheehan et al., 2006) is a semi-structured diagnostic assessment of DSM-5 psychiatric illnesses. The M.I.N.I. is efficient, reliable, and well-validated.

Assessment of Depression and Related Symptoms

Hamilton Depression Rating Scale (HAM-D) (Appendix): The HAM-D (Hamilton, 1960) is a is a clinician-administered scale considered to be the "gold-standard" means of assessing symptom severity in depressed patients. There are 21 items in this measure, but the total score is the sum of the first 17 items. Items assess common symptoms of MDD including mood, guilt, suicide, insomnia, work and activities, agitation, anxiety, and sexual interest.

Center for Epidemiological Studies Depression Scale – Revised (CESD-R) (Appendix): The CESD-R (Eaton et al., 2004) is a revised version of the *Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977).* It is a 20-item self-report symptom severity measure of depression. Patients endorse one of the answer choices (*Not at all or less than 1 day, 1-2 days, 3-4 days, 5-7 days, nearly every day for 2 weeks)* for each of the statements that list certain behaviors or feelings common to depression (in the past week). For example, items address appetite, sleep, weight, suicide, self-harm, attention, happiness, and interest. Participants will complete this form at baseline, midpoint, endpoint, and follow-up timepoints.

Clinical Global Impression – Improvement Scale (CGI-I) and severity scale (CGI-S) (Appendix): The single-item CGI-I, which ranges from 1 (very much improved) to 7 (very much worse), is commonly used in clinical trials (Guy, 1976). Participants will complete a CGI-I for MDD symptoms (CGI-P MDD) and the clinician will complete a CGI-I for MDD symptoms (CGI-MDD) and overall symptoms (CGI-global). The CGI-I ratings will be secondary outcome measures and will also be used to determine clinical deterioration of MDD via weekly administration through REDCap (link to be sent via email or in-app message) (see Minimizing Risks, below). The CGI also has a severity scale (CGI-S) which is rated by the clinician at baseline as well as the following assessments. The CGI-S determines the patient's overall level of symptom severity, in comparison to other patients the clinician has treated or assessed with the same diagnosis.

Patient Health Questionnaire-9 (PHQ-9) (Appendix): The PHQ-9 (Spitzer, Kroenke, & Williams, 1999) is a self-report measure of depression severity includes 9 Likert scale items ranging from 0 (*not at all*) to 3 (*every day*). The PHQ-9 will be used as an initial screening measure to determine symptom severity for inclusionary purposes, as well as at the midpoint, post-treatment, and 3-month follow-up assessments.

Patient Health Questionnaire-8 (PHQ-8) (Appendix): The PHQ-8 is a revised version of the PHQ-9 less item #9 (thoughts of death and self-harm). Research shows that the PHQ-8 is highly correlated with the PHQ-9 (> 99%) and shows highly similar sensitivity and specificity (Wu et al., 2020). It will be re-administered weekly prior to a patient's appointment with their study clinician. REDCap link to be sent via email or in-app message.

Columbia-Suicide Severity Rating Scale (C-SSRS) (Appendix): The C-SSRS (Posner et al., 2008) is a gold-standard, clinician-administered assessment of suicidal ideation and suicide behaviors. The baseline version, which assesses both lifetime and recent time frames, will be used to establish eligibility at the baseline/screening visit. The "Update" version, which assesses suicide risk since the last assessment, will be used at subsequent study administrations.

Depression, Anxiety, and Stress Scale (DASS-21): (Appendix). The DASS-21 is a 21-iitem self-report questionnaire created from a set of three self-report scales with 7 items each. The subscale groups include depression, anxiety, and stress scale (Lovibond & Lovibond, 1995).

Assessment of Functioning and Quality of Life

Work and Social Adjustment Scale (WSAS) (Appendix): The WSAS is a 5-item, self-report measure of impairment in occupational, social, and family domains (Mundt et al., 2002). Items are measured on 9-point Likert scales ranging from 0 (no impairment at all) to 8 (very severe impairment).

Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF) (Appendix). The Q-LES-Q-SF (Endicott, Nee, Harrison, & Blumenthal, 1993) is a 16-item self-report measure of subjective quality of life. Higher scores correspond with greater ratings of quality of life. The Q-LES-Q-SF has strong psychometric properties (Endicott et al., 1993).

Assessment of Expectancy, Motivation and Satisfaction

Credibility/expectancy questionnaire (CEQ) (Appendix): This 6-item, self-report, Likert-type questionnaire assesses patients' judgments about the credibility of the treatment rationale and treatment expectancy (Borkovec & Nau, 1972). It has good reliability (α=.81-.86), and validity is evident in its ability to differentiate between treatment rationales (Devilly & Borkovec, 2000).

The Client Satisfaction Questionnaire (CSQ) (Appendix) is an 8 item self-report questionnaire which assesses the satisfaction with clinical services received. It has excellent internal consistency and good discriminant validity (Attkisson, 2015).

University of Rhode Island Change Assessment Scale - Psychotherapy Version (URICA) (Appendix) is a 32-item Likert-type questionnaire that assesses how participants feel about starting and engaging in therapy (e.g., "I am doing something about the problems that have been bothering me."; McConnaughy, Prochaska, & Velicer,1983).

Other Assessments

Treatment History Medication, Treatment History Psychosocial, Treatment History Checklist forms (Appendix): These forms will be used to assess any medications taken within the last 2 months as well as any current or lifetime psychosocial treatment.

Lifetime Psychiatric Medication Form (Appendix)*:* This self-report form collects information about all lifetime psychiatric medications taken and will be administered at the baseline screening visit.

Concomitant medication and therapy form: (Appendix): This form probes for any changes in psychotropic medication and mental health treatments that the participant has made since the prior assessment. Any reported changes in therapy or medication are then logged in the CTHER or CMED logs.

Demographics Form (Appendix): This self-report form collects basic demographic data.

App Feedback Questionnaire (Baseline) (Appendix): This 3-item self-report questionnaire asks about participant's expectations of using the app (e.g., "How frequently do you intend to use Mindset?").

App Feedback Questionnaire (Midpoint) (Appendix): These multiple choice and open-ended questions ask participants to describe their ongoing perceptions of the app at midpoint (e.g., "How easy are the exercises to understand, overall?").

App Feedback Questionnaire (Endpoint) (Appendix): This self-report form collects participant feedback via multiple choice and open-ended questions pertaining to the content, usability, perceived usefulness, and aesthetics of the app (e.g., "How clear was the layout of the app?").

Mobile Application Rating Scale user version (uMARS) (Appendix): This self-report form collects participant evaluations of mobile health applications. Dimensions include engagement, functionality, aesthetics, and information quality.

Treatment Utilization Questionnaire (TUQ) (Appendix): This 3-item self-report form measures how much time participants are practicing treatment skills both on and off the app.

Technologist Interview Notes (Appendix): This interview guide asks about credibility/expectancy, client satisfaction, and improvements at post-treatment.

Life Events Questionnaire (Appendix): This question will be used to assess whether any major life events occurred since the previous assessment that might have had a psychological impact on the subject.

Therapist Satisfaction Questionnaire: (Appendix). This self-report form for clinicians will assess their satisfaction with using this app treatment approach.

Everyday Discrimination Scale Short Version: (Appendix). This 5-item self-report form asks about participants' experiences with discrimination in their daily life (Sternthal, Slopen, & Williams, 2011).

Adverse Event Form and Log (AE Form) (Appendix). This form probs for any major events or concerns (i.e., adverse events) since the last time the form was filled out.

Self Help Questionnaire: (Appendix) This self-report form collects information about any additional self-help behaviors that could have impacted their well-being or depression since beginning treatment.

IE Training and Qualifications, and Procedures to Ensure Assessment Integrity and Interrater Reliability: Assessments will be conducted by an IE who has a Master's or Doctoral degree in clinical psychology or related mental health field. The IE will be otherwise uninvolved in study procedures. Training and reliability checks will be done to ensure that IEs conduct ratings in a uniform way. IEs will first receive instruction in the MINI and HAM-D from a gold-

standard expert rater, prior to beginning as an IE. The IE will be supervised at minimum twice monthly. The IE will be required to demonstrate reliability on the HAM-D at a criterion of .80 ICC, compared to measures rated by a gold-standard rater. All assessments will be audiotaped for reliability ratings. To reduce rater drift, a trained reliability rater meeting the same qualifications as the IE will review 15% of randomly selected audiotaped interviews. If reliability falls below .75, we will institute retraining procedures.

Table 1 Assessment Measures by Occasions for the Open Trial.

Measure	Baseline	Baseline Re-assess	Weekly	Mid-Treatment Assess (wk 4)	Post-Treatment Assess (wk 8)	3-month Follow-up
Treatment History Checklist	✓					
Treatment History Medication	✓					
Treatment History Psychosocial	✓					
Life Events Question		✓		✓	✓	✓
AE Form		✓		✓	✓	✓
CONCOM Form		✓		✓	✓	✓
MINI	✓					
HAM-D	✓	✓		✓	✓	✓
C-SSRS Lifetime	✓					
C-SSRS Update		✓		✓	✓	✓
CGI–S	✓	✓		✓	✓	✓
CGI–MDD, CGI-Global		✓		✓	✓	✓
Technologist Interview Notes						✓
Demographics	✓					
Lifetime Psychiatric Medication Form	✓					
PHQ-9	✓	✓		✓	✓	✓
CGI-P (MDD)		✓	✓	✓	✓	✓
PHQ-8			✓			
CEQ	✓			✓		
URICA	✓					

CESD-R	✓			✓	✓	✓
Q-LES-Q-SF	✓			✓	✓	✓
WSAS	✓			✓	✓	✓
DASS-21	✓			✓	✓	✓
Everyday Discrimination Scale	✓			✓	✓	✓
Self Help Questionnaire	✓				✓	✓
CSQ				✓	✓	
Treatment Utilization Questionnaire				✓	✓	✓
App Feedback Questionnaire (Baseline)	✓					
App Feedback Questionnaire (Midpoint)				✓		
App Feedback Questionnaire (Endpoint)					✓	
uMARS					✓	
Therapist Satisfaction Questionnaire					✓	

If more than ten days elapse between a patient's initial baseline screening assessment and the start of treatment, the study IE would re-administer select forms, including an additional HAM-D form.

Despite our best efforts to retain participants, we do expect dropouts. Except for subjects who withdraw consent to participate, all who are withdrawn or drop out of the study will be asked to complete all scheduled assessments and we will provide remuneration for participation in assessments.

In addition to the assessment measures in Table 2, de-identified data from sensors in participants' mobile phones will also be collected via the CBT and Habits apps, to inform design and improvement of the app.

B. Drugs to be used

Not applicable

C. Devices to be used

Participants will download the CBT for MDD and Habits apps onto their personal smartphone devices.

D. Procedures, surgical interventions, etc.

Not applicable

E. Data to be collected and when the data will be collected

See above for the assessment schedules and assessment batteries for each phase.

VI. BIOSTATISTICAL ANALYSES

The IE and the RAs will play the primary role in data entry. Data will be entered in REDCap, a HIPAA-compliant, Partners-approved platform for electronic data capture that streamlines data collection and management, and ensures data integrity, resulting in improved data quality and reduced costs. For more information on REDCap, please see section IX, "Monitoring and Quality Assurance."

Dr. Susanne Hoeppner will be responsible for data management and analysis. All project staff will receive training in data management and data confidentiality procedures. Data checks will be done regularly to assure that all forms are entered and available for analysis. Questions or problems will be resolved promptly by communication between study staff. Data and analysis files will be backed up on the lab server and may also be stored in separate locked cabinets.

To characterize our sample, data will be displayed graphically, and summary statistics (e.g., means and frequencies) will be calculated for all variables, including demographic and clinical descriptors (e.g., from the MINI).

Prior to data analysis, all major variables will be screened for inconsistent or abnormal values. Continuous measures will be assessed for skewness and outliers (based on model residuals), and, if needed, will be transformed to better meet modeling assumptions of normality and homogeneity of variance. A two-tailed p-value $<.05$ will be considered evidence of statistical significance for the primary and secondary outcomes.

A. Specific data variables being collected for the study (e.g., data collection sheets)

Specific variables being collected, and their timeline are presented in Table 1, and described in the Study Procedures section.

B. Study endpoints

Primary endpoints: Feasibility and acceptability of the combined digital CBT plus virtual treatment.

Hypothesis 1a: We hypothesize that digital CBT plus virtual treatment will be feasible (based on uptake, engagement and drop-out rates).

Hypothesis 1b: We hypothesize that digital CBT plus virtual treatment will be deemed acceptable both to patients and clinicians (based on descriptive statistics of patient

expectancy and satisfaction, app use, app feedback, clinician ratings, as well as qualitative feedback).

Secondary endpoints: Preliminary efficacy of digital CBT plus virtual treatment for primary outcomes (i.e., reduction in severity of depressive symptoms) and secondary outcomes (e.g., quality of life at post-treatment, social and occupational functioning at post-treatment).

Hypothesis 2a: We hypothesize that participants receiving digital CBT plus virtual treatment will evidence statistically significant reductions in HAM-D scores from baseline to post-treatment (week 8).

Hypothesis 2b: We hypothesize that participants receiving digital CBT plus virtual treatment will evidence statistically significant improvement on secondary clinical outcome measures (i.e., functional impairment (WSAS) and quality of life (Q-LES-Q)) from baseline to post-treatment (week 8).

C. Statistical methods

Primary endpoints: feasibility and acceptability of the combined digital CBT plus virtual treatment.

Analysis:

We will examine feasibility (H1a) and acceptability (H1b) by reporting:

1. Refusal and dropout rates and reasons
2. Patient satisfaction, as measured by the Client Satisfaction Questionnaire
3. Patient feedback, as measured by Mobile Application Rating Scale user version
4. Patients' credibility and expectancy ratings for the open-label treatment, as measured by the Credibility/Expectancy Questionnaire
5. Treatment utilization, as measured by the Treatment Utilization Questionnaire

Secondary endpoints: preliminary efficacy of digital CBT plus virtual treatment for reducing severity of depression symptoms, and improving quality of life and functional impairment

Analysis:

Intention-to-treat mixed model analyses with repeated measures (baseline, mid-treatment, post-treatment) will be used to examine differences between pre- and post-treatment depression (HAM-D scores), using a two-tailed α-level of .05. The pre- to post-treatment effect size will be calculated. Similar analyses will also be conducted for change in functional impairment (WSAS) and quality of life (Q-LES-Q) over the course of treatment. We will not adjust for multiple testing among secondary outcomes based on the recommendation of Cook and Farewell (1996), who argue that multiplicity adjustments are not necessary if separate test results are interpreted marginally and address different aspects of the patient experience and decision-making process rather than alternative assessments of efficacy.

D. Power analysis

With n=28, we will have > 80% power to detect pre- to post-treatment effect sizes of $d \geq 1.37$ (very large effect sizes). The estimate of the detectable effect size is based on a single degree of freedom contrast in a paired means test, implemented in SAS for Windows version 9.4. The

power model used a two-sided alpha=0.05, a power of 0.80, assumed a pre- to-post-treatment correlation of 0.18, and a doubling of the standard deviation from pre- to post-treatment. The pre- to post-treatment correlation estimate was based on the mean pooled correlation between pre-test and post-test HAM-D scores in 14 CBT trials for adult depression (Cuijpers et al., 2016); with higher pre-post correlations, smaller effect sizes would be detectable in other secondary outcomes. The anticipated increase in outcome standard deviation was based on observations reported in treatment studies with participants with MDD, which reported pre- to post-treatment standard deviation increases in observed HAM-D scores in the range of 161-191% (Jarrett et al., 1999; Elkin et al., 1989; Goldberger et al., 2011). We further assumed no drop-out by the end of treatment, similar to what we observed in pilot studies for similar app-treatment for body dysmorphic disorder (Wilhelm et al., 2020); if drop-out was 20%, we would only be able to detect effect sizes of $d \geq 1.55$. For comparison, in a meta-analysis of randomized controlled treatment trials that included internet CBT (iCBT) for persons with MDD (Andrews et al., 2018), the observed median percentage of participants randomized who finished the treatment course was 66% (50/64 trials) and the interquartile range was 29% (Q1 52%, Q3 80%). Large pre-to post-treatment effect sizes for CBT treatments among patients with MDD are to be expected, based on a meta-analysis by Cuijpers and colleagues (2016), which found that the mean pre-post standardized mean difference (i.e., effect size) in 14 CBT trials was 1.79, 95% CI: [1.37, 2.21].

VII. RISKS AND DISCOMFORTS

A. Complications of surgical and non-surgical procedures
Not applicable

B. Drug side effects and toxicities
Not applicable

C. Device complications/malfunctions
If the app or supporting therapist dashboard malfunctions or does not work for a period of time, the patient may be unable to use the app to receive treatment or communicate with their therapist. Similarly, if the therapist dashboard were inaccessible, the therapist would not be able to communicate via the app with the patient. These risks could result in minor harms to users such as inconvenience or a delay in treatment. To mitigate risks of a temporary device malfunction, participants are given the study staff and investigators' contact information in the consent document. Thus, the clinical and study staff can communicate with the participant by phone call instead of through the app. As with in-person therapy, there are times when a therapy session gets cancelled and treatment, as well as weekly symptom assessments, are thus temporarily delayed. Likewise, in face-to-face therapy, a therapist may be temporarily out of reach at times (e.g., on vacation) and backup lines of communication (e.g., pager coverage by a colleague) are put in place in case of emergencies. Thus, device malfunctions that lead to temporary delays in accessing the app functionality are similar to risks associated with temporary delays in traditional face-to-face therapy. See also, "Minimizing of Risks and Safety Reporting" under "D. Psychosocial (non-medical) risks" for further description of protections in place.

D. Psychosocial (non-medical) risks
Participants may feel uncomfortable due to the sensitive nature of the questions they may be asked. Likewise, some participants may feel uncomfortable about having assessment sessions digitally recorded and reviewed by project staff (which is necessary for rater supervision as well as assessment of the reliability of ratings adherence and competence). Participants could experience an increase in symptoms related to the natural waxing and waning of MDD symptoms. MDD can be associated with other psychiatric symptoms (e.g., anxiety), as well as suicidal thoughts and behaviors, which may also change over time. Breach of confidentiality, which great care will be taken to prevent, represents a potential risk. As discussed below, we will take precautions to ensure that these potential risks are minimized (see Adequacy of Protection Against Risks below).

Privacy and Confidentiality

All information gathered will be kept strictly confidential. We will adhere to the following procedures to protect privacy and confidentiality:

1) Participants will be assigned a code number. A link between ID number and participant's names will be kept in a separate secure password-protected file, saved on our secure MGH lab server and/or Partners Dropbox Business. Participants' names or other identifying information will not appear on any questionnaires, study documents, digital recordings, computerized data files, or published reports. Case records will be reviewed only by study personnel or, if necessary, by institutional or sponsor-assigned regulatory personnel. Research assistants and others working on this study (e.g., technologists) will be educated about the importance of strictly protecting participants' rights to confidentiality.

2) All personnel will be trained in research confidentiality procedures and HIPAA, including completion of CITI training and Healthstream training. Only the study personnel (or, if necessary, institutional or sponsor-assigned regulatory personnel) will have access to the identifiable data.

3) Clinical data collected during MGH assessments: Computerized data and digital audio files will be stored de-identified, in password protected files saved on the protected lab server. Data within Partners is stored automatically and securely on an MS SQL Server, accessed over industry standard SSL 128 bit RSA encryption during data transfers. Data is routinely backed up locally onto a redundancy server and stored in a separate database that is locked with 256 AES encryption. Long term storage on Partners servers occurs nightly and allows for incremental backup over multiple systems. Therefore, should one drive be physically damaged, there will be multiples within the chain to replace it. Both data servers are stored within PHS IS corporate firewall, in a secure, key access facility with password protected computers. Only trained PHS security officials will have access to physical machines storing study data. Since data are stored on a protected server, a compromise of any individual computer at a research facility will not lead to a breach of the secure database. Hard copy data (paper forms) will be stored securely in locked file cabinets, within locked offices in the MGH Center for OCD and Related Disorders.

4) Technologist data: Computerized data and digital audio files collected from feedback interviews with technologists will be stored de-identified, in password protected files in the Partners Healthcare Dropbox Business folder. The PHS Dropbox Business folder will be set up by a listed owner with a Partners email address. Per Partners Research Information Services and Computing, "The enterprise rollout of Dropbox Business at Partners HealthCare is an approved storage and collaboration solution. This version of Dropbox Business provides unlimited storage, fully encrypted data (AES-256 encrypted) and is compliant with Partners' policies and procedures. Dropbox Business allows you to sync, share, and manage your files online" (https://rc.partners.org/kb/article/2285).

5) Mobile data: All mobile data will be transmitted from the participant's mobile device to the secure Mindset server (managed by Koa Health via public cloud service) via an encrypted internet connection. The collected data will be linked to the study identifier only. The administrative interface to the clinical study server (channels 1 and 7 below) will be password protected with access limited to study staff.

6) Habits: The Habits app and platform will be used to collect passive smartphone data. Habits is a secure, HIPPA-compliant research platform developed by Koa Health. Habits includes (a) a database inside the app container to store de-identified data, with nothing in shared storage, (b) a participant-facing app, and (c) a data analysis pipeline that pre-processes raw mobile data into daily aggregations. The current version of Habits has passed an internal security audit, and the data uploaded to the Koa data lake is stored in the same way as events collected from the Mindset app. The data is restricted to be accessed only by the researchers involved in the study and all the processing is done within the restricted access, HIPAA-compliant Amazon Web Services (AWS) server. In addition to the assessment measures in Table 2, de-identified data from sensors in participants' mobile phones will also be collected via the Habits app, to inform design and improvement of the app. Key features are summarized below:

- The participant does not need to register as a user. The participant will be provided a generated code with a unique study prefix and a non-identifiable string of numbers and letters after.
- Participants can only download and use the study's Habits app if given proper instruction from the study investigator (e.g., once fully consented and determined to be eligible).
- All data are stored with the de-identified user ID. No identifying data such as name or contact information are tied to participants' data. The only identifier that will be inputted into habits are dates.
- The app caches information locally (temporarily or if there is no connectivity). Any data stored locally (cache or otherwise) is stored encrypted in a database inside the app container.
- The app will not integrate with other apps on the phone. The app will only integrate with Google Fit, which is not an app.
- The app updates automatically as long as the default option of auto update is enabled.
- All data stored on the phone are sent to the servicer over an encrypted TLS connection to ensure the security of the data transmitted. The data is received by the server and stored in an AWS S3, an industry-standard secure storage platform housed in data centers that are protected by armed guards.

- All data connections to the web service hosting the study are negotiated on industry-standard SSL/TLS connections, removing the vulnerability of man-in-the-middle attacks or packet-sniffing data leaks.

6) All virtual visits (i.e., assessments with the IE and telehealth sessions with the therapist) will be conducted via a Partners IS-approved, secure, and HIPAA compliant system for video calls (e.g., Zoom).

7) Only de-identified data will be shared with the sponsor (Koa Health), under the terms of the Data Use Agreement (i.e., Statement of Work).

See Figure 1 and 2 in "Independent Monitoring of Source Data" for a detailed diagram and description of the secure data flow and storage.

Minimizing of Risks and Safety Reporting.

The following procedures will be implemented to protect participants against risks.

1. Participants with active suicidal ideation at the screening assessment will be excluded from participating (see Inclusion/Exclusion criteria). Suicidal ideation at screening is captured with the PHQ-9 #9 and the C-SSRS (see Inclusion/Exclusion criteria); if a potential participant scores ≥2 on the C-SSRS, a study clinician, PI, or independent evaluator will conduct a risk evaluation with the participant and refer the participant to a higher level of care if clinically indicated.

2. The therapist will assess risk weekly during virtual appointments and refer the participant to a higher level of care if clinically indicated, consistent with routine clinical care. If a patient unexpectedly does not attend their weekly session, the clinician, PI, or the independent evaluator will follow up with a phone evaluation within 24 hours and refer the participant to a higher level of care if clinically indicated.

3. A disclaimer that is accessible from the home page of the digital CBT program will be presented. The disclaimer will alert participants that "If you are having thoughts of suicide or death, please note that this program is not the right treatment for you. You should seek professional help without delay. If you feel unsafe, call 911 or go to your nearest emergency room." Links to 911 and suicide hotline numbers will be provided along with this disclaimer.

4. A general resources page will be available on the app at all times to participants, which will include a suicide hotline number.

5. Participants' clinical improvement or deterioration will be assessed weekly via a participant-rated CGI-MDD collected before each therapy session. Participants may be withdrawn from the study for a significantly deteriorating clinical course, as indicated by a score of 6 (much worse) or 7 (very much worse) on the weekly, participant-rated CGI-MDD, across 3 subsequent weeks and/or PI judgement that remaining in the study is not in the participant's best interest. Of note, study clinicians will review weekly CGI scores

and follow-up in session as appropriate. The clinician and/or PI will refer the participant to a higher level of care if clinically indicated.

6. Participants may also be withdrawn if, in the judgment of the PI, remaining in the study poses a substantial risk to the participant or a higher level of care is needed.

7. Treatment through app-based CBT will be supplemented with virtual visits with a therapist (8 sessions over the course of 8 weeks), who can answer questions and guide participants through the treatment as needed. These therapists will be doctoral level clinicians, or pre-doctoral interns supervised by doctoral-level clinicians, who are experts in CBT for MDD and related disorders.

8. The independent evaluator(s) will be highly experienced, highly trained, and closely supervised.

9. Dr. Wilhelm will be available, if necessary, to discuss the study, alternative treatments, or any concerns about the study with participants if requested by the participant, therapist, or rater.

10. Drs. Wilhelm, Greenberg, Bernstein, and the participants' study clinician will be available to answer study questions via the app or phone. This will be clearly communicated orally and in writing to study participants.

11. All participants who fail to respond to treatment or withdraw prematurely will be provided with referral resources.

12. The study therapists and raters will make every attempt to help participants feel comfortable when discussing sensitive material. Participants may skip questions on assessments that they are uncomfortable answering.

13. Technologists from Koa Health who conduct the technology feedback interviews are highly trained professional staff with experience conducting patient interviews and user-centered design. They have received additional training from our team (MGH Center for OCD and Related Disorders) on CBT, MDD, and issues of confidentiality. They have completed CITI training.

14. The subject will designate a relative or friend who could be contacted should the subject be unavailable, and the investigator has concerns about the subject's well-being.

We anticipate that the above procedures will be effective in protecting study participants against potential risks.

Adverse event reporting:
See below: "Adverse event reporting guidelines"

E. Radiation risks
Not applicable

VIII. POTENTIAL BENEFITS

A. Potential benefits to participating individuals
Participants may benefit from the comprehensive diagnostic assessment with a clinician assessor. Participants may benefit from careful clinical monitoring, sessions with their therapist, and experiencing some relief from their MDD symptoms through the CBT app.

B. Potential benefits to society
If the digital service combining app-based CBT for MDD with virtual visits with a therapist is effective, it may offer increased, cost-effective access to CBT for MDD, a treatment that is empirically supported and otherwise difficult to access.

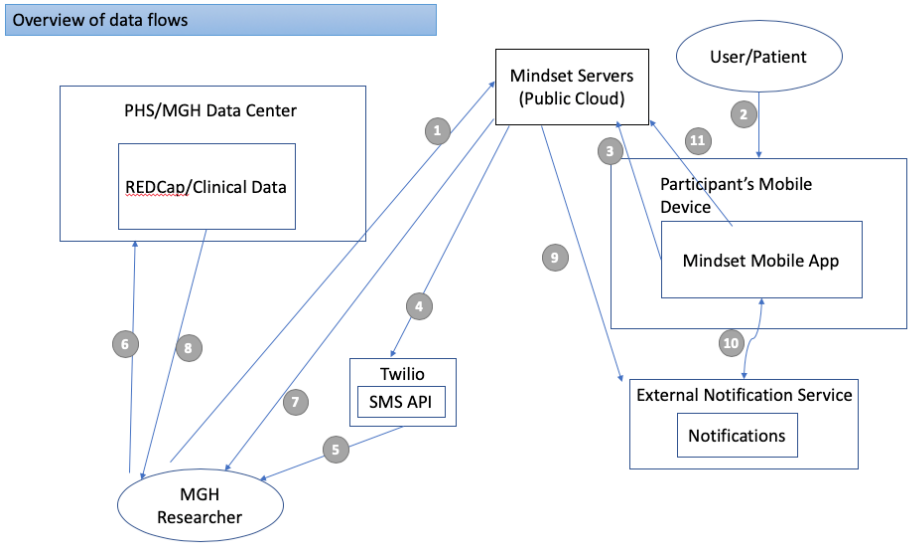
IX. MONITORING AND QUALITY ASSURANCE

Independent monitoring of source data
The PI will have overall responsibility for study data and participant safety. Please see "Privacy and Confidentiality" above for more information about the data collected for the present study including (1) Clinical data (formal assessments with the MGH IE, which includes self-report and audio recorded clinician-administered assessments completed on paper and via REDCap) (2) Mobile data (self-report questions collected electronically within the mobile app, and passively collected data through sensors in participants' mobile phones). All aspects of the study will be conducted in accordance with the hospital's policy on confidentiality.

Paper research records will be kept de-identified, in a locked file in a locked office at MGH. Self-report measures and some clinician administered measures will be collected using REDCap. REDCap (Research Electronic Data Capture) is a free, secure, HIPAA compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Data collection projects rely on a study-specific data dictionary built by members of the research team. Once built, participants and study staff can enter data directly into REDCap surveys via any computer or tablet with standard web access and browsers. To ensure confidentiality, data will be identified in the database solely by subject number, mapped patient initials (whereby each initial is replaced with the next letter in the alphabet), week number, and visit date (i.e., subjects' names will not be entered into the database). By identifying study records in this manner, the information can be considered 'de-identified' and therefore compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996 (HIPAA). Any data that is transmitted electronically will be encrypted and password protected. IEs will enter their clinical assessment data directly into REDCap, except for one form (i.e., MINI) that will first be collected as paper forms or as electronic records in PDF format. The electronic form of the MINI assessments will be completed by IEs using the Notability software on iPads, where the assessment data is entered using a stylus and the PDF record plus data is saved as a new PDF file. The completed PDF-copy of the MINI forms are then uploaded into the study-specific Partners Healthcare Dropbox Business folder designated for this purpose. One study staff

member (either the IE or a designated, trained RA) will then enter the data from the paper or PDF forms into the designated REDCap forms within 3-5 business days of the completion of the assessment visit, and another staff member (trained RA or undergraduate intern) will enter the same forms into double data entry records for data entry comparisons. If discrepancies are noted, the trained staff responsible for data entry will check the source documentation and correct the REDCap form as necessary. Data entry by participants for self-report measures in this electronic data capture system precludes the need for subsequent data entry by staff, thus minimizing human error, and resulting in improved data integrity and quality. Patients will enter survey responses into an electronic assessment form on subject-facing REDCap, and the responses will then be transmitted and stored in a secured and confidential database. Each participant will only have access to his or her own survey, but not the survey data. All users will have defined roles and privileges pre-determined by the system administrator. Thus, the PI can determine the level of access for each study staff such that only a limited number or people have access to sensitive study data. To protect patient privacy, when completing REDCap questionnaires, participants will be asked to enter their random codes in place of any identifying information (e.g., name, birth date). All identifying information will be stored separately from data in a password-protected file. Together with the data collected on paper forms or PDF records (i.e., MINI), Mindset app, and the Habits app (see sections "Privacy and Confidentiality" above for details), the data entered by IEs and RAs into REDCap will be considered the source documentation.

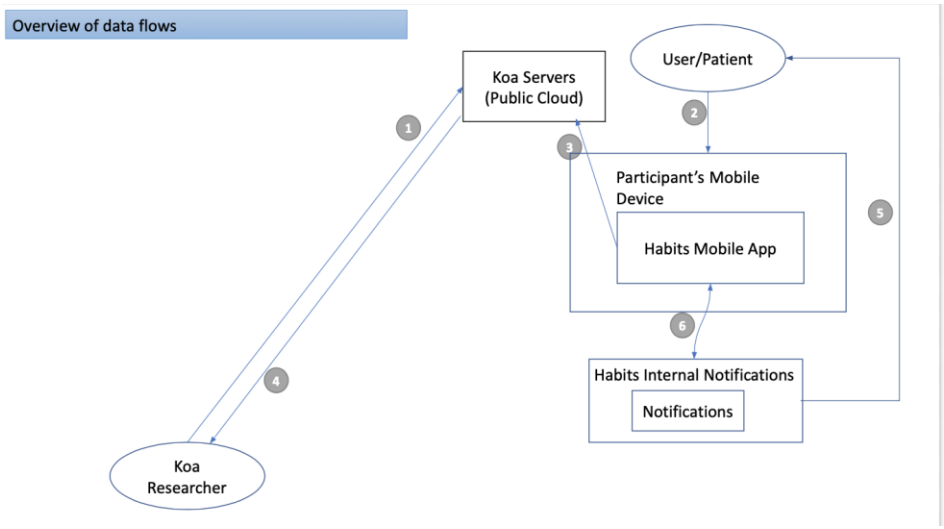
Figure 1. Data flow and storage chart. "Mindset" refers to the CBT for MDD mobile application.



1. Researchers have accounts on the Mindset Server (i.e., the CBT app) that allow them to create participant accounts (random IDs) that they then give to study participants.
2. Participants install mobile app on their mobile devices, then enter the activation code provided by MGH staff (e.g., clinician, therapist, RA) and grant access to receive push notifications.
3. The application collects and sends data such as:
    a. progress across the exercises,
    b. information about feature usage (analytics),
    c. answers to questionnaires.

4. N/A (function that will not be utilized in trial)
5. N/A (function that will not be utilized in trial)
6. Researchers collect additional information on subjects using REDCap
7. Researchers access the data collected via the mobile app, check user progress, communicates with the patient through integrated messaging.
8. Researchers pull data from REDCap
9. The server sends Push Notifications to notify the user when:
    a. The therapist has sent a message
    b. Data sent to an External Notification Service includes:
        i. The registration token identifying which device should receive notification
        ii. Textual content of the notification (title and body)
10. Application reaches out to the External Notification Service to:
    a. Register for Push Notifications. When registering the app sends a uniquely generated identifier that identifies the app installation.
11. All the info from potential app crashes are stored in mindset servers. Retrieved information includes:
    a. Device vendor
    b. Device model
    c. OS version
    d. Error details (stack trace)

Figure 2. data flow and storage chart. “Habits” refers to the passive data collection mobile application.



1. Researchers have accounts on the Habits Server that allow them to create participant identifier (random IDs) that they then give to study participants.
2. Participants install Habits mobile app on their mobile devices, then enter the participant identifier provided by research staff and grant access to receive notifications.
3. The application collects and sends data such as:
    a. sensing data coming from smartphone sensors (such as number of steps)

b. information about feature usage (analytics),
c. answers to questionnaires.

4. Researchers access the data collected via the mobile app on the Koa Servers and check user data.
5. (Optional) The user allows the app to send Notifications to notify the user when it is time to fill a weekly questionnaire. These are local notifications set up within the app which only include and send to the user: textual content of the notification (title and body)
6. (Optional) Habits sets Local notifications logic on when to send the notifications to users (e.g., every 2 weeks to fill a specific questionnaire)

We anticipate that the above procedures will ensure the confidentiality and integrity of study data.

C. Safety monitoring

The PI will have overall responsibility for monitoring the integrity of study data and participant safety. Procedures for managing participant safety, including the monitoring of participants throughout the trial and response to clinical deterioration (as defined above) should it occur, are detailed above in "**Minimizing of Risks and Safety Reporting.**"

D. Outcomes monitoring

Adverse events and data completeness will be monitored as described above.

E. Adverse event reporting guidelines

Adverse event reporting: Adverse events will be reported per PHRC guidelines.

X. REFERENCES

Andersson, G., Cuijpers, P., Carlbring, P., Riper, H., & Hedman, E. (2014). Guided Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: a systematic review and meta-analysis. *World Psychiatry, 13*, 288-295.

Borkovec, T. D,. & Nau, S. D. (1972). Credibility for analogue therapy rationales. *J Behav Ther Exp Psychiatry, 3*, 257-260.

Cook, R., & Farewell, V. (1996). Multiplicity Considerations in the Design and Analysis of Clinical Trials. Journal of the Royal Statistical Society. Series A (Statistics in Society), 159(1), 93-110. doi:10.2307/2983471

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *The Canadian Journal of Psychiatry, 58*, 376-385.

DeRubeis, R.J., Webb, C.A., Tang, T.Z., & Beck, A.T. Cognitive therapy. In: Dobson KS, ed. Handbook of cognitive-behavioral therapy. 3rd ed. New York: Guilford, 2010.

Devilly, G. J., & Borkovec, T. D. (2000). Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Exp Psychiatry, 31,* 47-55.

Endicott, J., Nee, J., Harrison, W., & Blumenthal, R. (1993). Quality of Life Enjoyment and Satisfaction Questionnaire: A new measure. *Psychopharmacology Bulletin, 29*, 321-326.

Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J., et al. (2013). Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from

the Global Burden of Disease Study 2010. PLoS Med 10: e1001547. https://doi.org/10.1371/journal.pmed.1001547

Goldberger, C., Guelfi, J. D., & Sheehan, D. V. (2011). Assessment of Anxiety in Clinical Trials with Depressed Patients Using the Hamilton Depression Rating Scale. Psychopharmacology bulletin, 44(3), 34–50.

Guy, W. (1976). Clinical Global Impressions. In W. Guy (Ed.), *ECDEU Assessment Manual for Psychopharmacology (*rev. ed.; DHEW publication [ADM] 76-338; pp. 217-222*)*. Rockville, MD: U.S. Department of Health, Education, and Welfare, National Institute of Mental Health.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry, 23*, 56-62

Hedman, E., Ljótsson, B., & Lindefors, N. (2012). Cognitive behavior therapy via the Internet: a systematic review of applications, clinical efficacy and cost–effectiveness. *Expert review of pharmacoeconomics & outcomes research, 12*, 745-764.

Kroenke, K. & Spitzer, R.L. (2002). The PHQ-9: A new depression and diagnostic severity measure. *Psychiatric Annals, 32*, 509-521.

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour research and therapy, 33*(3), 335-343.

McConnaughy, E.N., Prochaska, J.O., & Velicer, W.F. (1983). Stages of change in psychotherapy: Measurement and sample profiles. Psychotherapy: Theory, Research and Practice, 20, 368-375.

McMurtry, S. L. & Hudson, W. W. (2000). The Client Satisfaction Inventory: Results of an initial validation study. *Research on Social Work Practice, 10*, 644-663.

Mojtabai, R. (2005). Trends in contacts with mental health professionals and cost barriers to mental health care among adults with significant psychological distress in the United States : 1997–2002. *American Journal of Public Health, 95*, 2009–2014.

Mundt, J., Marks, I., Shear, M., & Greist, J. (2002). The Work and Social Adjustment Scale: A simple measure of impairment in functioning. *British Journal Of Psychiatry, 180*, 461-464.

Posner, K., Brent, D., Lucas, C., Gould, M., Stanley, B., Brown, G., ... & Mann, J. (2008). Columbia-suicide severity rating scale (C-SSRS). New York, NY: Columbia University Medical Center.

Rush, A. J., Trivedi, M. H., Ibrahim, H. I., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P. T., Kornstein, S. G., Manber, R., Thase, M. E., Kocsis, J. H. & Keller, M. B. (2003). The 16-item Quick Inventory of Depressive Symptomatology (QIDS) Clinician Rating (QIDS-C) and Self-Report (QIDS-SR): Psychometric evaluation in patients with chronic major depression. *Biological Psychiatry,* 54, 573–583.

Sareen J, Jagdeo A, Cox BJ, Clara I, ten Have M, Belik SL, de Graaf R, Stein MB (2007). Perceived barriers to mental health service utilization in the United States, Ontario, and the Netherlands. Psychiatric Services 58, 357–364.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E. ... Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry,* 59, 22-33.

Smith, A. (2017). Record shares of americans now own smartphones, have home broadband. *Pew Research Center.* url: http://www.pewresearch.org/fact-tank/2017/01/12/evolution-of-technology/

Sternthal, M. J., Slopen, N., & Williams, D. R. (2011). RACIAL DISPARITIES IN HEALTH: How Much Does Stress Really Matter? *Du Bois review: social science research on race, 8*(1), 95.

van Voorhees BW, Fogel J, Houston TK, Cooper LA, Wang NY, Ford DE (2006). Attitudes and illness factors associated with low perceived need for depression treatment among young adults. Social Psychiatry and Psychiatric Epidemiology 41, 746–754.

Webb, C. A., Rosso, I. M., & Rauch, S. L. (2017). Internet-based cognitive-behavioral therapy for depression: current progress and future directions. Harvard review of psychiatry, 25, 114-122.

Wilhelm S, Weingarden H, Greenberg JL, McCoy TH, Ladis I, Summers BJ, Matic A, Harrison O. Development and pilot testing of a cognitive-behavioral therapy digital service for body dysmorphic disorder. Behavior Therapy, Jan. 2020, 51(1):15-26. Doi: 10.1016/j.beth.2019.03.007

Wu, Y., Levis, B., Riehm, K. E., Saadat, N., Levis, A. W., Azar, M., ... & Thombs, B. D. (2020). Equivalency of the diagnostic accuracy of the PHQ-8 and PHQ-9: a systematic review and individual participant data meta-analysis. *Psychological medicine*, *50*(8), 1368-1380.