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Study Protocol for clinicaltrials.gov

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STUDY TITLE:
Digital Mental Health Service for Non-Treatment Seeking Adults

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RELATED STUDIES:
Preliminary design studies to inform the text messaging service
STU00213675, STU00209015, STU00211168.
Deploy the messaging service through MHA: STU00216348
Conduct user-centered design research to refine intervention and evaluate efficacy in randomized trial
Efficacy of messaging service for broad set of adults: STU00214828

Check any **applicable** boxes in the table below – you will be asked for further detail on these topics later in the protocol form:

Indicate Vulnerable Population(s) to be Enrolled	☐ Children ☐ Cognitively Impaired Adults ☐ Pregnant Women (IF the research activities will affect the pregnancy or the fetus) ☐ Prisoners (or other detained/paroled individuals)
International Research (check this box if you will collect data from individuals located outside the United States)	☐
Research involving external collaborators (some research activities will be carried out by	

individuals not employed by Northwestern or NU affiliates)	☐
Research has U.S. Federal government funding (e.g., NIH, NSF, other federal agencies/departments)	☒

1.0 Purpose and rationale of the study:

PURPOSE:

Young adults, aged 18-25, experience higher levels of mental health problems than any other adult age group. In any given year, 13% of young adults meet diagnostic criteria for a major depressive disorder and 22% for an anxiety disorder.[1,2] Untreated, these conditions can become chronic, more severe, or both, but early treatment and preventive interventions reduce risk of future episodes.[3–6] Unfortunately, young adults are unlikely to receive treatment. Average time from first symptoms to treatment is more than 8 years for young adults.[7,8] While structural barriers interfere with treatment access, most young adults experiencing mental health problems do not even want psychotherapy or psychotropic medication,[9] due to low mental health literacy, stigma, and a preference for self-reliance.[9–11] There is a disconnect between current mental health care needs and the ways in which young adults want to obtain help. While many are not interested in traditional treatment, they are interested in using digital technologies that provide information, guidance and skill building for self-management of their symptoms.[12–14] Digital mental health interventions (DMHIs) can effectively reduce symptom severity[15–17] and have the potential to increase access to care for young adults who would not otherwise seek out face-to-face treatments. However, maintaining engagement — necessary for DMHIs[18] — has been an ongoing challenge in the field.[19–21] The primary method of enhancing engagement has been human coaching,[20,22] which can be brief, focused on encouraging use, and has proven effective at improving engagement and outcomes.[20,23] Most DMHIs rely on mobile or browser-based apps, which require a user action to access the intervention. In contrast, SMS text messages arrive through the most commonly used app on the phone,[24] and are far more likely to be viewed.

The primary purpose of this project is to design and evaluate an 8-week automated, adaptive, text messaging (a.k.a. SMS) platform that addresses the shortcomings of other mental health interventions for young adults by providing messages that include psychoeducational content and encourage the development and use of Cognitive Behavioral Therapy- and Acceptance and Commitment Therapy-based strategies (e.g., behavioral activation, cognitive restructuring, valued living, etc.).

We will partner with Mental Health America (MHA), the nation's largest mental health advocacy organization, to design and pilot a highly personalized messaging intervention for depression and anxiety. We will use an iterative design and development process that provides a voice to end-users in message and content creation.[25] We will pilot our automated, adaptive DMHI against a randomized version of the intervention and against an active control using a sequential multiple assignment randomized treatment (SMART) design, which targets those disengaged users for additional human support. The *adaptive intervention* will be powered by reinforcement learning to deliver tailored SMS messages based on user profiles and the ways in which a user interacts with the intervention system, along with links to longer psychoeducational content. The *randomized intervention arm* will not personalize the messages, but will still be an active treatment. The *active control* will provide, via a URL, brief psychoeducational content, but will not include the messaging component.

This project has the following three overarching aims:

Aim 1. Develop an adaptive messaging service for young adults that personalizes messages and psychoeducational content to the needs and preferences of an individual.

Aim 2. Evaluate the feasibility of conducting a SMART trial in which 120 young adults screening positive for depression or anxiety on the MHA website will be randomized to receive the adaptive (personalized) messaging intervention, a randomized version of the intervention, or an active control condition. Participants who meet criteria for non-engagement with the messaging interventions during the first 2 weeks will be randomized to receive coaching or continue without coaching for the remaining treatment period. Feasibility criteria include successful recruitment of participants, attaining 80% completion of research assessments, and <30% treatment dropout in at least one treatment condition. We will pilot the following analyses:

Aim 2a. Evaluate the effectiveness of messaging interventions, compared to waitlist control, in reducing psychological distress and secondary outcomes (depression and anxiety symptom severity, suicidal ideation, openness to therapy, and interest in formal treatment), and engaging treatment targets (subjective and objective engagement, behavioral activation, dysfunctional attitudes, coping skill use).

Aim 2b. Evaluate the effectiveness of an adaptive vs. randomized messaging intervention to reduce psychological distress, increase engagement duration, improve secondary outcomes and targets.

Aim 2c. Evaluate the ability of coaching to improve engagement targets and psychological outcomes.

Aim 2d. Explore participant characteristics and factors associated with the need for human coaching support above and beyond a messaging intervention with randomized and adaptive messaging.

Aim 3: Experimental therapeutics: Explore if engagement targets (subjective and objective engagement) and psychological targets (behavioral activation, dysfunctional attitudes, coping skill use) mediate significant effects for distress observed in Aims 2a, 2b, or 2c.

BACKGROUND:

Most young adults with mental health diagnoses do not seek out in-person mental health care. While young adults are the age group with the highest prevalence (26.3%) of mental health problems, they are the adult age group with the lowest rates of treatment.[26] Without early intervention, their symptoms tend to become worse and more chronic.[3–6] We know that digital mental health interventions are effective at reducing affective symptoms,[15,16] and young people are interested in these interventions.[27]

Young adults use digital technologies regularly: 96% own a smartphone, and they are the age group most likely to access the internet exclusively through their smartphone.[28] Thus, smartphones are a medium with high penetration through which to deliver a digital mental health intervention. Meta-analyses[15,16,29] have consistently shown that mobile app and browser-based DMHIs can be effective at reducing symptoms of anxiety and depression across randomized controlled trials.[29] While DMHIs are effective when used, they often produce high dropout.[20,21]

The vast majority of DMHIs have used mobile apps or browser-based interventions, which requires the user to open an app that is used solely for mental health management. Thus, users, whose conditions often include decreased motivation and increased avoidance, must remember and take time out to engage with an app. In contrast, text messaging is now the most commonly used communication medium, exceeding phone, email, and social media, and the dominance of text messaging is greatest among young adults.[30] Text messaging is widely available, even in places with limited internet access.[31] Text messaging fits easily into the fabric of people's lives, delivering messages with no effort on the part of the user through a highly utilized communication pathway. For pure messaging interventions, it is not possible for researchers to see if a text message has been read and therefore, it can be difficult to measure adherence. However, one study, focused on young adults, found 84% overall compliance with daily mood ratings,[32] indicating high adherence. While the

effects on depression did not reach significance, overall satisfaction with the messaging program was high. Thus, messaging appears to be an accessible and acceptable method, however effectiveness remains inconsistent.

There are several reasons we believe messaging alone has been inconsistent in producing symptom reduction in mental health. First, while messages are good for providing prompts, encouragement, or single pieces of information, their brevity makes them ill-suited to convey more complex information, such as a treatment rationale. We have found in our work that providing somewhat longer pieces of psychoeducational content helps contextualize messages, making them more useful for users. The proposed intervention will integrate messages with psychoeducational content, accessible via a URL embedded in a text message. There are two additional strategies for improving engagement and effectiveness that are the focus of this research: personalization and coaching.

We use personalization to refer to the process of automatically tailoring messages and prioritizing content to meet the needs and preferences of individuals. In mental health, personalization that has employed baseline user characteristics such as age, gender, marital status, and symptoms to select content and messages have shown modest benefit.[33] However, these strategies essentially target subpopulations and are not responsive to context or fluctuating states or symptoms. Digital interventions are known to be more effective if personalization occurs throughout the intervention, incorporating new information to adapt to the individual's preferences and needs.[34,35] To accomplish personalization, we will use machine learning techniques such as reinforcement learning and multi-armed bandit models[36,37] to discover which actions (e.g., versions of message content) are best for different user characteristics, and other states that are collected over the course of an intervention (e.g., message ratings, link clicks, symptoms, etc.). Providing a user with the most relevant psychological strategy and the right communication strategy should produce stronger engagement, resulting in better clinical outcomes.

Coaching involves human provisioned support, typically delivered by telephone or messaging (e.g., email or text). Coaching is believed to work in part by establishing a relationship that provides support and accountability.[38] A large number of studies have demonstrated that coaching improves both intervention use[20] and mental health outcomes.[29] While we expect that our messaging intervention will be engaging, we must also anticipate that there will be a group of users who will not engage. We therefore will explore the potential benefit of adding coaching to our messaging platform. Our SMART trial design identifies participants, who become disengaged from either the randomized or adaptive intervention early in treatment, and evaluates whether adding low-intensity human supportive coaching can effectively re-engage participants. We will explore participant characteristics associated with the need for low-intensity coaching, which may facilitate the scalability of messaging interventions.

STUDY ENDPOINTS

This protocol describes procedures for two separate, but related, studies:

1. Design Studies
    a. Longitudinal Usability Testing
2. Clinical Trial

*[NOTE: AS OF 3/27/23, WE ARE PREPARED TO ROLL OUT UPDATED PROCEDURES FOR THE CLINICAL TRIAL IN ADDITION TO LONGITUDINAL USABILITY TESTING]

2.0 Enrollment Criteria (who can be in your study and who would not be eligible to participate in your study):

(1) Longitudinal Usability Testing

Inclusion criteria for the MHA sample are:

1) Ages 18-25*; the age to provide consent in Nebraska is 19. Individuals recruited from the state of

Nebraska must be 19 or older.
2) A positive screen on an MHA screen for depression (Patient Health Questionnaire – 8 [PHQ-8] ≥ 10[39]) or anxiety (Generalized Anxiety Disorder - 7 [GAD-7] ≥ 10[40])
3) Resident of the United States.
4) Owns a smartphone

Exclusion criteria for the MHA sample are:

1) Is currently receiving psychotherapy, or intends to begin therapy over the next 8 weeks
2) Has initiated or had a dose change for an antidepressant medication within the previous 4 weeks or intends to change the dose
3) Serious mental illness for which intervention would be contraindicated (e.g., psychotic disorder, manic episode, etc.)*
4) Severe suicidality (i.e., experiencing suicidal ideation with a plan and intent to act; less severe suicidality will not be exclusionary);
5) English insufficient to engage in design activities.

*If a participant indicates they are uncertain of a Bipolar diagnosis the research team may follow-up with the participant to clarify and determine their eligibility

Inclusion criteria for the CBITs registry sample are:

1) Ages 18 or over (ages 19 or over for individuals recruited from the state of Nebraska).
2) A positive screen for depression (Patient Health Questionnaire – 8 [PHQ-8])
3) Resident of the United States
4) Owns a smartphone

Exclusion criteria for the CBITs registry sample are:

1) Is currently receiving psychotherapy, or intends to begin therapy over the next 8 weeks
2) Has initiated or had a dose change for an antidepressant medication within the previous 4 weeks or intends to change the dose
3) Serious mental illness for which intervention would be contraindicated (e.g., psychotic disorder, manic episode, etc.)
4) Severe suicidality (i.e., experiencing suicidal ideation with a plan and intent to act; less severe suicidality will not be exclusionary)
5) English insufficient to engage in design activities

(2) Clinical Trial:

Inclusion criteria are:

1) Ages 18 to 25 *The age to provide consent in Nebraska is 19. Individuals recruited from the state of Nebraska must be 19 or older.
2) A positive screen on an MHA screen for depression (Patient Health Questionnaire – 9 [PHQ-9] ≥ 10[39]) or anxiety (Generalized Anxiety Disorder - 7 [GAD-7] ≥ 10[40]);
3) Resident of the United States.
4) Owns a smartphone

Exclusion criteria are:

1) Is currently receiving psychotherapy, or intends to begin therapy over the next 8 weeks
2) Has initiated or had a dose change for a psychiatric medication within the previous 4 weeks or intends to change the dose in the next 8 weeks.
3) Current elevated symptoms of serious mental illness for which intervention would be contraindicated (e.g., psychotic disorder, manic episode, etc.)
4) Severe suicidality (i.e., experiencing suicidal ideation with a plan and intent to act; less severe

suicidality will not be exclusionary);
5) English insufficient to engage in study activities.
6)
VULNERABLE POPULATIONS: N/A

3.0 Sample Size:

1. Design Studies
    a. Longitudinal Usability Testing -- We will enroll up to a total of 40 participants in up to 4 waves to use the adaptive messaging intervention.
2. Clinical Trial – With 40 participants randomized to each group, we will have 80% power to to detect an effect size of *d*=0.64 for the treatment vs. control compassion. The effect sizes related to messaging interventions for depression have not yet been tested across enough trials to estimate effect sizes. However, meta-analyses comparing coached DMHIs to control conditions have shown effect sizes of *g*s=0.67-0.70 for depression and anxiety, which is not significantly different from psychotherapy.[41] Effect sizes for self-guided DMHIs and smartphone interventions are considerably smaller (*g*s= 0.27-0.43).[42,43] It should be noted that choice of control condition can have a substantial impact on effect sizes. For coached DMHIs, the effect-size for trials using WLCs is *g*=0.90, while effect sizes for studies using active controls is understandably smaller, *g*=0.38. [41] Thus, we would expect to see an effect size of approximately *d*=0.38 for treatment vs. control, as these analyses will pool participants across both engaged participants, who do not require a coach, and coached participants. While we acknowledge this effect size is lower than the effects we are powered to detect, it serves as a useful benchmark in determining whether the intervention shows sufficient value to pursue a larger trial.

    As the use of machine learning to personalize messages is novel, there are no studies that provide ideal guidance as to the expected effect size for the adaptive vs. randomized intervention comparisons for DMHIs. However, there is considerable research using "computer-tailored" messaging for health behaviors (e.g. smoking cessation, physical activity, diet, mammography). A meta-analysis showed effect sizes of *g*=0.12-0.22 for tailored vs. randomized messaging.[35] These algorithms are simpler that those proposed here, typically consisting of decision trees that tailor only on baseline participant characteristics. Based on this literature, we would expect an effect size of approximately *d*=0.20 in analyses comparing the randomized and adaptive arms. Such an effect size would warrant the inclusion of the proposed machine learning algorithms to personalize messages to meet the needs and preferences of users.
    a. Active Control Group (n=40)
    b. Automated Intervention (n=40)
    c. Randomized Intervention (n=40)

4.0 Recruitment and Screening Methods:

(1) Longitudinal Usability Testing;

The sample will be recruited from two sources:

1) Up to n=20 will be recruited from Mental Health America (MHA). MHA is a non-profit organization whose mission is to address the needs of those living with mental illness, prevent psychological decompensation, and to promote mental health as a crucial component of general health. MHA will support recruitment by displaying an IRB approved clickable teaser advertisement (See advertisement text uploaded to eIRB+) for the current study to individuals who complete the PHQ-9 or GAD-7 on their screening website and meet our criteria of PHQ-8 or GAD-7 of 10 or higher. MHA will not be engaged in the research or have access to any identifiable information gathered through this study.

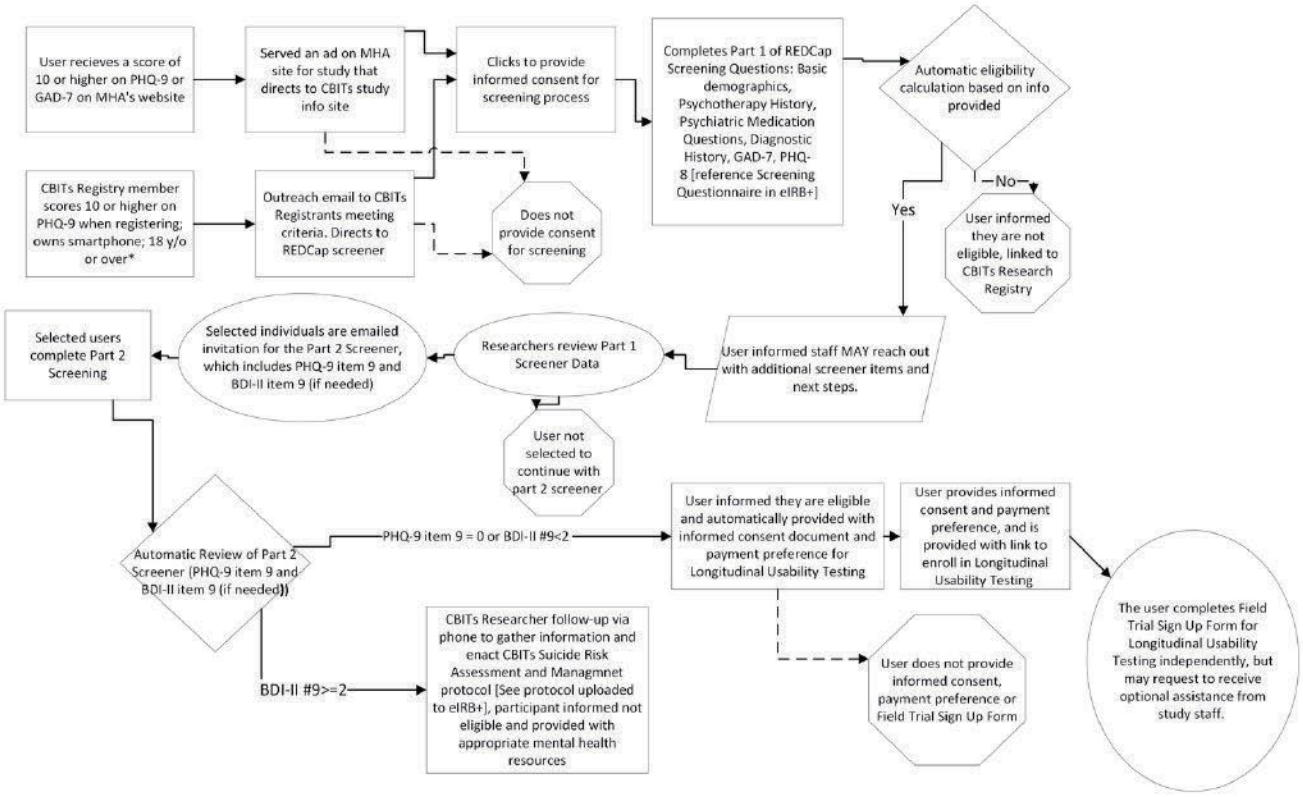
Individuals can elect to click the advertisement if they are interested in learning more about the study. This ad will direct interested individuals to read an IRB approved description of the study that will be hosted on the Center for Behavioral Intervention Technologies (CBITs) website (see website text uploaded to eIRB+). The study description will contain a link to review a screening consent form and initiate on online screener to determine eligibility. [procedures for eConsent and screening continued below]

2) Up to n=20 will be recruited from the CBITs Research Registry. Outreach emails (See Outreach Email uploaded to eIRB+) will be sent to members of the CBITs research registry meeting the following criteria: (1) Ages 18 or older, or 19 or older for individuals in Nebraska, (2) upon joining the registry, obtained a PHQ-8 score of 10 or greater, and (3) owns a smartphone. Individuals who receive the outreach email and are interested in participating can click a link in the outreach email that will take them to an on online screener to determine eligibility.

[eConsent and screening Procedures] Regardless of recruitment source, a two-step screening procedure will be implemented (see Figure 1 below for detailed participant flow). After providing informed consent for the screening procedures, individuals will complete a screening questionnaire on REDCap (see uploaded screening questionnaire in eIRB+), which assesses demographic information, psychiatric treatment history information, smartphone ownership information, and plans for psychiatric treatment. It will also include the GAD-7 and PHQ-8. After completion of the Part 1 Screener, preliminary eligibility will be automatically calculated. Individuals not meeting eligibility criteria will be informed and will be offered a link to learn more about our CBITs Research Registry. Those meeting preliminary eligibility will be informed that responses will be reviewed and they may be selected to complete additional screening steps. Researchers will email selected individuals meeting Part 1 eligibility criteria a link to a REDCap screener containing the PHQ-9 item number 9 and, if needed, an item from the BDI-II which asseses suicidal intent [See section 17 on Protecting Against Risks to Participants]. Once an individual completes the PHQ-9 item 9 and any required follow-up items from the BDI-II. Eligibility will be automatically calculated. Individuals who do not endorse suicidal ideation + intent to act will be automatically directed to the informed consent document for the study and given the opportunity to provide their informed eConsent. If two days after an eConsent form has been sent out, a participant has not provided informed consent or reached out to study staff, CBITs researchers will follow-up via phone, email or text message.

Individuals with elevated suicidal ideation and intent to act will be contacted by research staff for risk assessment and management according to the procedures detailed in section 17 of this document [Protecting Against Risks to Participants]. Participants will be informed they are not eligible for the current study and provided with appropriate mental health resources. This two step process enables research staff to meet possible demand for risk assessment follow-up procedures by limiting the number of individuals completing the PHQ-9 item 9 at any one time during the screening process.

Following provision of affirmative informed consent, participants will be sent a link to a payment preferences form (see Payment Preferences for in eIRB+) the sign-up form that, once completed, will initiate automated text messages from the messaging system. Participants will simultaneously be sent instructions on how to complete the sign-up form [see eIRB+ for SIGN-UP FORM], which requests basic information required to deliver text messages (e.g., cell phone number, preferred start and end times for messages, etc.) and initial preference data that will enable messages to be tailored via machine learning algorithms (e.g., detailed demographic information, content topic preferences, K10 items, etc.]. Participants will have the option to request synchronous instruction from study staff on how to complete the sign up form and initiate text messages. If an individual has consented to study procedures, but not initiated text messages by completing the sign-up form, research staff will reach out to the participant to offer assistance.



(2) Clinical Trial:

1) Up to n=120 will be included and enrolled from Mental Health America (MHA). MHA is a non-profit organization whose mission is to address the needs of those living with mental illness, prevent psychological decompensation, and to promote mental health as a crucial component of general health. MHA will support recruitment by displaying an IRB approved clickable teaser advertisement (See advertisement CLINICAL TRIAL text uploaded to eIRB+) for the current study to individuals who complete the PHQ-9 or GAD-7 on their screening website and meet our criteria of PHQ-8 or GAD-7 of 10 or higher. MHA will not be engaged in the research or have access to any identifiable information gathered through this study. Individuals can elect to click the advertisement if they are interested in learning more about the study. This ad will direct interested individuals to read an IRB approved description of the clinical trial that will be hosted on the Center for Behavioral Intervention Technologies (CBITs) website (see website CLINICAL TRIAL text uploaded to eIRB+). The study description will contain a link to review a screening consent form and initiate on online screener to determine eligibility. [procedures for eConsent and screening continued below]

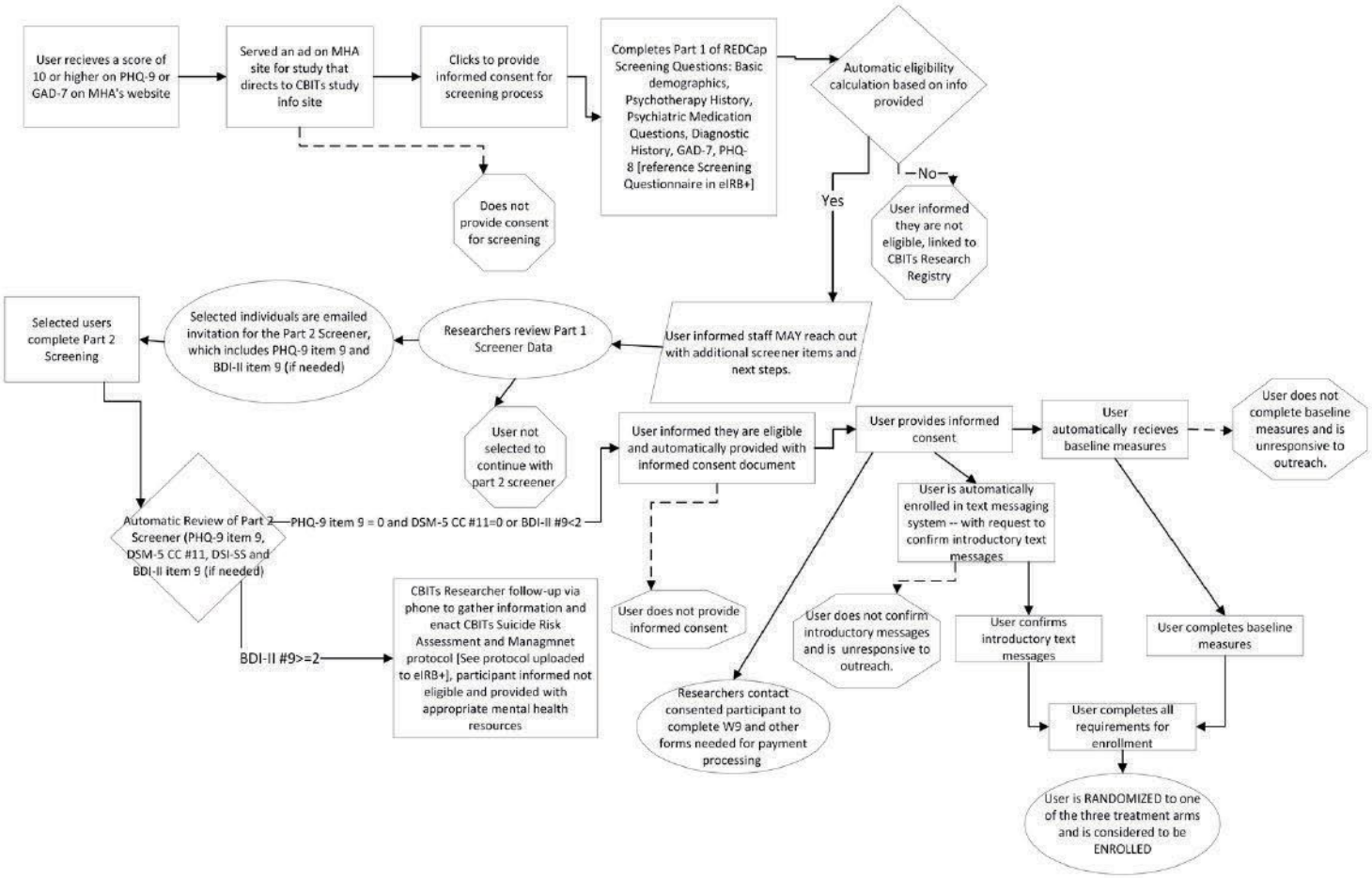
[eConsent and screening Procedures] A two-step screening procedure will be implemented (see Figure 1 below for detailed participant flow). After providing informed consent for the screening procedures, individuals will complete a screening questionnaire on REDCap (see uploaded CLINICAL TRIAL screening questionnaire in eIRB+), which assesses demographic information, psychiatric treatment history information, smartphone ownership information, and plans for psychiatric treatment. It will also include the GAD-7 and PHQ-8. After completion of the Part 1 Screener, preliminary eligibility will be automatically calculated. Individuals not meeting eligibility criteria will be informed and will be offered a link to learn more about our CBITs Research Registry. Those meeting preliminary eligibility will be informed that responses will be reviewed and they may be selected to complete additional screening steps. Researchers will email selected individuals meeting Part 1 eligibility criteria a link to a REDCap screener containing items assessing suicidal thoughts (I.e., the PHQ-9 item number 9, DSM-5 Cross Cutting Symptom measure item #11, and the DSI-SS and, if needed, an

item from the BDI-II which assesses suicidal intent [See section 17 on Protecting Against Risks to Participants]). Once an individual completes Part 2 of our screening process, eligibility will be automatically calculated. Individuals who do not endorse suicidal ideation + intent to act will be automatically directed to the informed consent document for the study and given the opportunity to provide their informed eConsent. If two days after an eConsent form has been sent out, a participant has not provided informed consent or reached out to study staff, CBITs researchers will follow-up via phone, email or text message.

Individuals with elevated suicidal ideation and intent to act will be contacted by research staff for risk assessment and management according to the procedures detailed in section 17 of this document [Protecting Against Risks to Participants]. Participants will be informed they are not eligible for the current study and provided with appropriate mental health resources. This two-step process enables research staff to meet possible demand for risk assessment follow-up procedures by limiting the number of individuals completing the PHQ-9 item 9 at any one time during the screening process.

Following provision of affirmative informed consent, participants will be automatically directed to baseline questionnaires. They will also be sent a payment preferences form (see Payment Preferences form in eIRB+), depending on the payment preference selected, a W9 form that requires a signature may be sent (via an electronic signature platform such as DocuSign), and participants will be signed up for the text messaging system which will initiate brief introductory text messages.

Users will be required to respond to these introductory messages to confirm they were received and they will also need to complete the baseline assessment measures before being enrolled in the trial. Once confirmation of text message receipt is obtained and baseline measures are completed, participants will be randomized to one of three trial arms. Only once randomization occurs, participants be considered enrolled. Participants may request research staff assistance at any stage of the enrollment process. If, at any point, a potential participant has not completed one of the required steps (e.g.,confirmation of text messages, completion of baseline measures), research staff will conduct outreach to resolve the issue, and answer any questions. Research staff will also follow-up with participants who have incomplete payment forms.**Outline of participant recruitment and enrollment flow, below:**



5.0 Research Locations:

(1) Longitudinal Usability Testing; (2) Clinical Trial:

All study procedures will be performed at Northwestern University via online platforms and all assessments delivered via Northwestern University administered REDCap surveys.

6.0 Multi-site Research (research that involves external collaborating institutions and individuals):

N/A

7.0 International Research (where data collection will occur outside the United States and U.S. territories)

N/A

8.0 Procedures Involved:

Please check the boxes for all applicable data collection procedures you plan to use:

☒One-on-one interviews

☐Focus Groups

☒Questionnaires/surveys

☐Analysis of secondary data (medical record data, educational records, government or private sector datasets, etc.)
☐Ethnographic observation
☐Physiological measurements (e.g., EEG, EKG, MRI)
☐Biospecimen collection (saliva samples, blood draws, hair samples, etc.)
☒Mobile applications/data collection devices (e.g., Fitbits, actigraphs, etc.)
☐Behavioral decisionmaking tasks (e.g., puzzles, interactive games, etc.)
☐Physical activities such as walking and other forms of exercise
☐Other procedures (briefly list types of procedures here if not covered by the check-boxes above):
_____

8.1 Procedures

DESIGN STUDY
The design study utilizes UCD processes to be conducted at Northwestern University, by recruiting participants via Mental Health America's website and via the CBITs Research Registry. These design activities will test prototypes of the SMS messaging intervention. Following an iterative software development process our UCD process consists of longitudinal usability testing. This will also involve up to two participant interviews after approximately 4-weeks of system use (Waves 1 and 2) and after completing 8-weeks of system use (Wave 1 only).

Longitudinal usability testing:

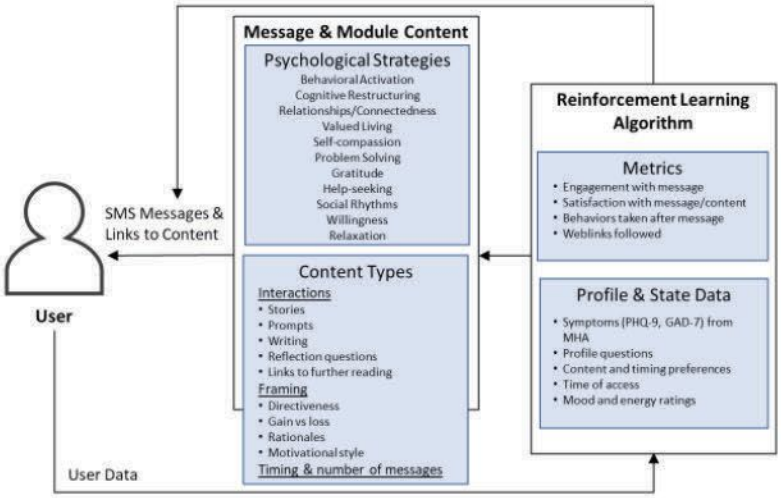
We will obtain feedback on the overall usefulness and acceptability of the messaging intervention design through longitudinal remote usability testing which has been used to evaluate platform and software usability.[44,45] We will enroll up to 40 total participants for up to 8-weeks (depending on the wave of data collection) to use the adaptive messaging intervention. The first wave of enrollment will consist of up to 20 individuals (all have been enrolled between 8/25/22 and 10/19/22) who will use the intervention for 8 weeks. The second wave of data collection (to begin after 11/1/22) will involve using the intervention for up to 4-weeks. Up to a total of 4 waves of participants allow for the research team to make iterative corrections and improvements to the messaging intervention based on feedback from previous waves. A staggered enrollment process allows enough time for the research team to make iterative design adjustments and deploy them in a timely manner. Longitudinal usability testing also allows us to leverage participant use/non-use data to identify usability problems and develop personalized interview questions that will help identify potential usability problems. Participants will participate in a telephone or videoconference interview at up to two points during the longitudinal usability testing: after 4 weeks of system use (Waves 1 and 2) and after 8 weeks of system use (Wave 1 only). Interviews will last no more than one hour and will be audio recorded and transcribed. Interviews are semi-scripted, such that we touch on certain high priority topics and questions, but also may deviate from the script to ask follow-up questions based on users' responses. Interviews will elicit qualitative feedback about the acceptability and usefulness of the messaging intervention, allowing us to understand the nature of problems encountered.

1. After providing informed consent to participate, and completing the self-guided onboarding process in which participants will learn how to interact with the intervention, how to provide feedback, and complete a sign-up form that, once completed, will initiate automated text messages from the messaging system [see eIRB+ for SIGN-UP FORM].
2. Researchers will review system use logs and message logs to inform interview questions (see next step)
3. Participants will be asked to complete 20-60 minute telephone or videoconference-based semi-scripted interviews at the end of weeks 4 (Waves 1 and 2) and 8 (Wave 1 only). These timepoints enable the research team to obtain qualitative data about early use (week 4) and

sustained use (week 8).

4. Users will also be asked to take screenshots and maintain error logs or feedback to send to the research staff between interviews.
5. Qualitative data will be coded using thematic analysis[46] and will examine any differences in usability across race, ethnicity, gender, and recruitment source. Features and usability problems identified through interviews will be considered in need of attention and candidates for modification. Problems will be identified and corrected in an iterative manner.
6. Researchers will employ a safety monitoring protocol to automatically flag incoming messages that may signal possible safety concerns, research staff will conduct risk assessments and management as needed [see detailed safety monitoring and management procedures in Sec. 17.0 Risks to Participants].

The architecture of the platform is described below and can be viewed in figure 1 (below):



The intervention system consists of interactive messages, which comprise 11 psychological strategies as well as various interaction styles.

8.1.1 Messages:

Messages are the primary form of engagement. Participants in the *randomized* version will receive approximately 4-10 messages per day that target different psychological strategies and types of interaction styles. Participants in the *adaptive* version also receive messages that target psychological strategies and types of interaction styles, but the system will be powered by reinforcement learning algorithms that will deliver tailored content based on participants' ratings and response patterns.

8.1.1.1Psychological strategies:

Text messages will provide brief background information on the strategy and how it can help, with elaboration available at the user's convenience through web content. Each day of content centers on a small skill or activity that fits within the strategy. The user is encouraged to apply each new skill or activity in daily life.

Psychological Strategy	Brief Description and Application
Behavioral Activation	Increases contact with rewarding activities. Messages supporting behavioral activation may prompt the user to: 1) identify an activity that has potential to

	bring the user pleasure or a sense of accomplishment, 2) make a plan to do that activity, and 3) notice changes in mood that accompany doing the activity.
Cognitive Restructuring	Centers on noticing and changing negative thought patterns. Messages supporting cognitive restructuring prompt the user to: 1) notice which automatic negative thoughts recur, 2) create a record of those thoughts, and 3) come up with re-framings of negative thoughts.
Social Connectedness	Increases outreach and bids for connection with others to elicit social support and strengthen relationships. Messages supporting social interaction prompt the user to: 1) identify people who bring positive value into the user's life, 2) show appreciation to those people, and 3) schedule activities that involve positive social contact.
Problem Solving	Focuses on identifying problems and systematically choosing optimal solutions. Messages supporting Problem solving prompt the user to 1) identify and articulate a specific problem, 2) generate possible solutions, 3) evaluate solutions relative to potential gains and drawbacks
Willingness	Aimed at increasing a users ability to experience a full range of human experiences without selectively avoiding unpleasant experiences. Messages supporting willingness prompt the user to 1) identify experiences that have been actively avoided due to fear of discomfort, 2) Generate ways to approach this experience with openness and non-judgmental observation, 3) evaluate efforts to practice a willing stance.
Valued Living	Assists uses in identifying and moving toward overarching forces or themes users find meaningful. For example, messages supporting valued living focus on 1) psychoeducation on the distinction of values from goals, 2) ways to articulate and identify meaningful themes or forces, 3) practice constructing concrete objectives and actions that are consistent with a user's identified values
Social Rhythms	Helps users establish and maintain daily routines. Messages focused on social rhythms prompt the user to 1) identify any daily routines that work well for them, 2) try several types of new routines centered around sleep, meals, or other daily occurrences, 3) evaluate the effect of practicing routines on their affective state.
Gratitude	Involves practicing an appreciative stance. Messages focused in this area are designed to help a user 1) notice things, people, experiences, that bring a user a sense of gratitude, 2) notice how gratitude affects mood and anxiety, 3) document aspects of their lived experience that they appreciate.
Relaxation	This strategy is designed to help users reduce physical and emotional tension. Messages focused on relaxation are designed to 1) familiarize users with basic brief relaxation techniques, 2) notice how relaxation impacts mood and anxiety symptoms, 3) identify when practicing relaxation may benefit a user.
Self-Compassion	Centers on building awareness of self-criticism and increasing users' psychological flexibility with regard to process of change and growth. Messages in this area prompt a user to 1) notice harsh self-critical thoughts, 2) practice a gentler self-narrative, 3) track progress over time.
Help Seeking	Aims to decrease some barriers to formal and informal mental health support. Messages focused on help seeking 1) provide information on types of treatment

	options or available support (both formal and informal), 2) link to and show ways of using informational resource hubs that connect would-be-patients to providers, 3) provide psychoeducation and practice prompts for how to identify and trusted others users may decide to disclose mental health concerns to for the purpose of eliciting support and connection to care.

8.1.1.2Interaction Types:

1) *Prompts* provide psychoeducation around a psychological strategy, skill, or principle (e.g., "Self-compassion is a technique that involves acting kindly and gently towards oneself, even if we make mistakes or are feeling down"). Prompts also support a user applying the strategy, skill or principle, to their own life and context (e.g., " The next time you are being hard on yourself, notice the language you use."), and may include open-ended questions to the user (e.g., "What's one way you could be kinder to yourself?").
2) *Stories* include brief narratives that illustrate a peer addressing a challenge by applying a psychological principle or skill (E.g., "Here's one person's story of struggling to find motivation: I woke up this morning and just didn't want to face the day. I had to write several emails for work, and finish putting together a presentation"…")
3) *Writing* dialogues ask users to write messages for the purpose of supporting others when they are feeling down, low, or depressed. Writing prompts (e.g., "Please help us write a short message that might motivate someone who feels depressed. What would you say to help them to get through a bad day?") are sent to users and followed by questions that give users the option of sharing their messages with others or with themselves later on (e.g", "Would you like us to send this message to you next time your mood is low or you're having a hard day?"). Before being shared, any messages that users wish to share will vetted by the research team to screen for biased or stigmatizing language, identifiers, or any content that might be harmful for others (e.g., explicit details around self-harm or suicide).
4) *Links* provide additional relevant reading, viewing, or listening that illustrates a concept introduce through the messaging system. Links to additional reading, video and audio content provides a diverse set of content to users.
5) *Modular* dialogues enable users to cycle through many brief interactions in a relatively short period of time. They may take the form of reflection questions, supportive messages, peer stories, or actionable brief prompts. For example, "If you are struggling to find something to be thankful for, you can always start small. It can be a supportive friend, a useful tool, a clean shirt, or a good meal. What is one thing that makes your life better?" or "When do you feel the most motivated?"

8.1.2Adaptive Intervention:

Content types, psychological strategies, message timing, and frequency will by adapted based on a machine learning (multi-arm bandit) algorithm built into the messaging system. Content preferences such as message satisfaction (e.g., 5-pt Likert scale rating of how much the user liked the message/content), engagement rates (e.g., how recently or frequently a user responds to the intervention messages), link clicks (whether a user clicks a link sent in a message) will be used to evaluate content preferences and power the machine learning algorithms.

8.1.3 Coaching (Wave 2 participants ONLY):

Participants in this wave (Wave 2) of longitudinal usability testing will receive human support in the form of digital coaching. Participants will be assigned to a digital coach who will send periodic text messages or conduct other forms of outreach (e.g., email, phone, videoconference) to the participant to help the participant engage in the intervention and apply tools from the intervention to their daily

contexts. Digital coaching for mental health interventions is based on both the efficiency model of support and the supportive accountability model. According to the Supportive Accountability Model[38] in combination with the Efficiency Model,[47] adherence to behavioral intervention technologies (BITs), as well as adoption of new skills gained from BITs can be enhanced when participants have some level of human support to bridge gaps in (1) usability — how easy it is to actually use the intervention due to any technical challenges; (2) fit — how well an intervention actually addresses a participants's needs or goals; (3) knowledge — lack of health literacy or important conceptual misunderstandings that lead to unexpected or improper use of the intervention; (4) implementation — failure to translate skills gained while using an intervention to everyday life.

Human support can address each of these issues in targeted ways, but at a minimum needs to provide participants with accountability — or the presence (physical or virtual) of another human being. When accountability is provided to participants in a manner that is supportive, this accountability can help bridge natural waning in users' motivation, address technical and knowledge issues, improve intervention fit, and help users translate lessons to their everyday life. As part of the intervention, we provide participants with a coach — a trained expert in the Small Steps intervention who can help the participant engage with the intervention, apply skills from the intervention to their everyday life, and work with the participant to support their goals and enhance their motivation to use the intervention. The coach will also provide positive reinforcement and praise when users engage with the intervention in ways that support their goals and meet their needs.

Coaches will follow the guidelines below throughout their interactions with participants to achieve these aims.

1) Build rapport and trust, support participant choice and autonomy, and set clear expectations about the coaching role in supporting the participant to achieve their goals.

2) Guide and support the participant in pursuing activities that support symptom self-management.

3)Monitor progress, identify failure points, and communicate these to the participant.

Measures:

During longitudinal usability testing data will be gathered from patients as outlined in the table below.

Depression symptoms	Patient Health Questionnaire-9 (PHQ-9)	10-item measure assessing depression symptom severity	Self-report	Baseline and weeks 4, and 8 (Wave 1 only)
Generalized anxiety disorder symptoms	Generalized Anxiety Disorder-7 (GAD-7)	8-item measure assessing GAD symptom severity	Self-report	Baseline and weeks 4, and 8 (Wave 1 only)
Usability	System Usability Scale (SUS)	10-item measure of usability and usefulness	Self-report	Week 4 and Week 8 (Wave 1 only)
	Usability Satisfaction and Ease of use (USE)	30-item measure that assesses three aspects of usability	Self-report	Week 4 and Week 8 (Wave 1 only)
Perceptions of messaging	Custom measure	Evaluations of messages' supportiveness, relevance, informativeness, repetitiveness (e.g., "How supportive were the messages you received from the messaging program? 1=not at all supportive;7=extremely supportive")	Self-report	Week 4 and Week 8 (Wave 1 only)
Suicidal Intent	Beck Depression Inventory #9	Item assessing intent of acting on suicidal plans	Self-report	As needed
Suicide Risk	Columbia	Multi-step clinical interview	Clinical	As Needed

	Suicide Severity Rating Scale (C-SSRS)	designed to assess suicide risk	Interview	
Semi-scripted feedback Interviews	Audio recorded user feedback interview	See topic outline	Clinical Interview	Week 4 and Week 8 (Wave 1 only)
System Use	N/A	messages responded to and rated, link clickthroughs, etc. will be monitored via message and server logs	N/A	Continuous

CLINICAL TRIAL

Clinical Intervention

We will conduct a clinical trial of our Small Steps intervention which is described below under **Small Steps Intervention Design**. Briefly, The Small Steps intervention consists of 8-weeks of text messages that integrate diverse evidence-based psychotherapy techniques and brief psychoeducational content to users. Messaging provides brief interactions that serve to keep the psychological strategies and goals in the user's mind, while psychological content, which is also brief, provides context for the messages. The clinical trial design is described below under **Clinical Trial Design**, but briefly the trial will include 3 arms, an active psychoeducational control arm, an *adaptive* version that will use machine learning to personalize message number, timing, and content, and a *randomized* version which will be the same intervention as the adaptive version, but will not use any machine learning or personalization. For individuals randomized to the adaptive or randomized versions of the Small Steps Intervention and who show signs of early disengagement (described below) in the first 2 weeks of use, participants will be re-randomized to receive human supported coaching.

Small Steps Intervention Design

The intervention system consists of interactive messages, which comprise 11 psychological strategies as well as various interaction styles.

Messages:

Please reference Section 8.1.1, *8.1.1.1, and 8.1.1.2, above for a description of messages, psychological strategies, and interaction types that will be used in the Small Steps Intervention Design.*

1) Decision Engines:

Adaptive Intervention:
Content types, psychological strategies, message timing, and frequency will be adapted based on a machine learning (multi-arm bandit) algorithm built into the messaging system. Content preferences such as message satisfaction (e.g., 5-pt Likert scale rating of how much the user liked the message/content), engagement rates (e.g., how recently or frequently a user responds to the intervention messages), link clicks (whether a user clicks a link sent in a message) will be used to evaluate content preferences and power the machine learning algorithms.

Randomized Intervention:
The randomized treatment will use the same intervention as the Adaptive Intervention, except that it will not use machine learning for personalization but instead use a randomization engine that will give equal weight to all potential content decisions.

Coaching:
Coaching involves human provisioned support, typically delivered by telephone or messaging (e.g., email or text). Coaching is believed to work in part by establishing a relationship that provides support and accountability.[38] A large number of studies have demonstrated that coaching improves both intervention use[20] and mental health outcomes.[29] While we expect that our messaging intervention will be engaging, we must also anticipate that there will be a group of users who will not engage. We therefore will explore the potential benefit of adding coaching to our messaging platform. Among those randomized to receive a messaging intervention, participants who become disengaged during the first 2 weeks of the intervention, will be re-randomized at the time they are determined to have disengaged to receive either (a) coaching, to help support engagement, in addition to continued randomized or adaptive messaging, or (b) continued adaptive or randomized messaging via SMS without coaching, depending on the participant's original intervention assignment.

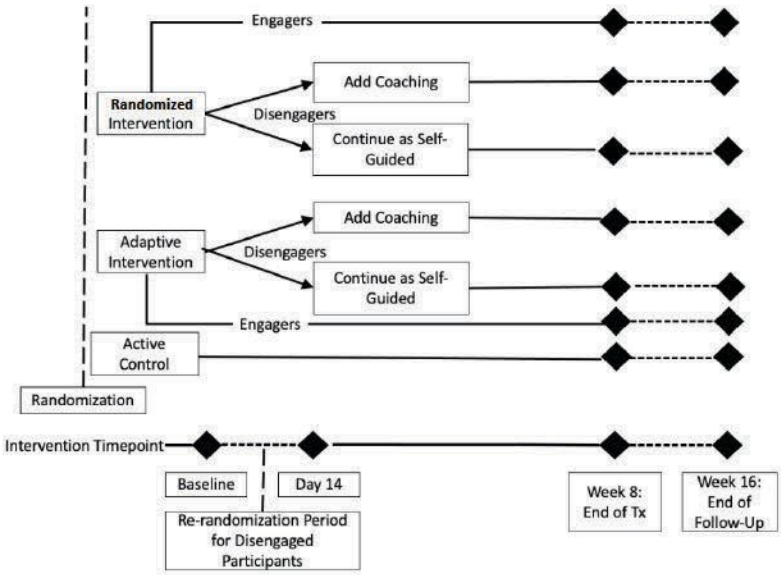
Disengagement will be defined as 3 or more non-continuous days of not responding to messages, rating messages, or completing symptom assessments. Any single action will be considered evidence of continued engagement.

Treatment Arms:
Adaptive Intervention: The adaptive intervention will be powered by reinforcement learning to deliver tailored SMS messages based on user profiles and the ways in which a user interacts with the intervention system, along with links to longer psychoeducational content.
Randomized Intervention: The randomized treatment will use the same intervention as the Adaptive Intervention, except that it will not use machine learning for personalization.
Active Control (AC): In the Active Control group participants will receive psychoeducational text messages, (up to 3 on each of the 11 psychological strategies), but these messages will not include interactive messaging (i.e., messages that require a response or action from the user other than reading or clicking on a link to learn more about a particular psychological strategy). Some messages will contain a URL link that contains information about psychological strategies that may be helpful for managing symptoms of depression and anxiety proposed messaging interventions.

Clinical Trial Design:
The clinical trial will utilize a SMART trial design (see Figure below). Participants will be recruited from MHA's website. The first level of randomization is to one of the three treatment conditions: (1) active control (n=40), adaptive intervention (n=40), or randomized intervention (n=40). This level of randomization will provide us with preliminary data on 1) the effectiveness of messaging as an

intervention and 2) the effectiveness and engagement of randomized vs. adaptive versions. The second level of randomization occurs following disengagement (as defined above under "Coaching" within the first two weeks of intervention use). Participants who meet the disengagement criteria from either the randomized or adaptive intervention will immediately be randomized to receive coaching or continue as self-guided. This data will provide us with preliminary information on the need for and value of coaching (Figure below).

Figure. SMART Trial Design



User feedback: When a participant concludes the intervention (up to 10 participants from each treatment combination [e.g., randomized intervention no coaching; randomized intervention + coaching; adaptive intervention no coaching; adaptive intervention + coaching), they will be asked to engage in a 30-45-minute user feedback interview, to identify problems and deficiencies with the aim of improving the intervention. Participants who discontinue the intervention will be contacted for an interview at the time their discontinuation is confirmed.

Assessment Strategy:
The primary outcome is psychological distress, measured using the Kessler Psychological Distress Scale (K10).[49] Administration will occur as part of the research protocol via REDCap online. The primary intervention target is engagement length, measured by time from 1st message sent to the last data point obtained via SMS. Secondary outcomes include: depression, measured by the PHQ-9;[39] anxiety, measured by the GAD-7;[50] suicidal ideation, measured by the DSI-SS;[51,52] and openness to seeking psychological care, measured by the Attitudes Toward Seeking Professional Psychological Help Scale-Short Form (ATSPPH-SF).[53]

Data will be gathered from patients as outlined in the table below.

Table of Study Assessments and Assessment points

			Study Week						
Construct	**Measues**	**Brief Description**	**Screening**	**0**	**1**	**4**	**8**	**12**	**16**

N/A	Screener	Demographics, treatment history, message preferences, timing, topic interest, etc.	X						
Psychological Distress	*Kessler Psychological Distress Scale (K10)	10-item self-report measure of transdiagnostic distress	X			X	X	X	X
Subjective engagement	Twente Engagement with eHealth Technologies Scale (TWEETS)	9-item self-report measure assessing cognitive, behavioral, and affective engagement with a digital tool			X	X	X	X	X
Cognitive behavioral coping	***Cognitive Behavioral Response to Stress Scale (CB-RSS)	9-item self-report measure of behavioral and cognitive coping related skills		X		X	X	X	X
Depression symptoms	** Patient Health Questionnaire-9 (PHQ-9)	10-item self-report measure assessing depression symptom severity	X			X	X	X	X
Generalized anxiety disorder symptoms	**Generalized Anxiety Disorder-7 (GAD-7)	8-item measure assessing GAD symptom severity	X			X	X	X	X
Suicidal ideation	***Depression Symptom Inventory - Suicidality Subscale (DSI-SS)	4-item self-report questionnaire assessing the frequency and intensity of suicidal thoughts over previous two weeks		X		X	X	X	X
Openness to seeking psychological care	Attitudes Toward Seeking Professional Psychological Help Scale-Short Form (ATSPPH-SF)	10-item self-report measure assessing a) openness to seeking treatment for emotional problems and b) value and need		X		X	X	X	X

		in seeking treatment							
Supportive Accountability	Supportive Accountability Index (SAI) [NOTE THIS IS ONLY FOR PEOPLE RANDOMIZED TO COACHING]	A 6-item self-report measure that assesses elements of the supportive accountability model of human support in digital mental health treatments				X	X		
Cross cutting symptom severity inventory	DSM-5 Cross-Cutting Symptom Measure*	Brief Cross-Cutting symptom inventory assessing severity of different psychiatric symptoms	X			x	x		x
Helpfulness and supportiveness of messages	Message Perceptions Questionnaire	A custom 6-item self-report measure of supportiveness and helpfulness of messages.				X	X		
Usability	USE	Usefulness, Satisfaction, and Ease of Use Questionnaire (USE)				X	X		
Disability, health, and impairment	WHODAS 2.0	12-question, self-administered questionnaire and generic assessment instrument for health and disability		X			X		X
Social Anxiety Symptoms	BFNE	12-item self-administered questionnaire assessing fear of negative evaluation		x					
General Study managemetn	Group Assignment Check	A single item measure assessing which treatment arm the participant thinks they were in.					X		

Objective Engagement	Phone number and System Use/message Logs			Throughout

8.2 STUDY TIMELINE

DESIGN STUDY
Longitudinal Usability Testing

Participants will use the intervention system for up to 8 weeks (Wave 1 [n=20 individuals who completed the enrollment process between 8/25/22 and 10/19/22]) or up to 4 weeks (Wave 2 [individuals who complete enrollment process after 11/1/2022]) depending on the wave of data collection, complete assessments at baseline, weeks 4 (Waves 1 and 2), and 8 (Wave 1 only), and participate in feedback interviews lasting up to 60 minutes each at the end of weeks 4 (Waves 1 and 2) and 8 (Wave 1 only).

CLINICAL TRIAL
This trial will utilize a SMART design. Active participation will last 16 weeks for each study participant. Study assessment milestones are laid out in the Table of Study Assessments and Assessment points in the section above.

9.0 Research with Vulnerable Populations:

N/A

10.0 Incomplete Disclosure or Deception:

N/A

11.0 Consent Process

DESIGN STUDY
Longitudinal Usability Testing

[For Recruitment and Screening Procedures, please see Section 4.0]

1. Once an individual completes the Part 1 and Part 2 (PHQ-9 item 9 and any required follow-up items from the BDI-II) screening process and has determined to be eligible to participate in the study, Individuals will be automatically directed to the informed consent document for the study and given the opportunity to provide their informed eConsent. If two days after an eConsent form has been sent out, a participant has not provided informed consent or reached out to study staff, CBITs researchers will follow-up via phone, email, or text message

2. Once the consent form has been submitted, the staff will receive an electronic notification which will prompt him/her to confirm that the form was signed by the participant. If participants decline informed consent, their screener data will be retained for reporting purposes, but their screener information will not be used in future research unless they indicated willingness to be contacted for future research activities.

3. Once participants provide informed consent, they will be sent information about how to initiate intervention text messages and interact with the intervention prototype. Research staff will also reach out to participants to schedule the the 4-week follow-up interview with research staff.

4. REDCap reports will be generated daily to alert the study staff to follow-up with subjects who have not signed the digital consent form within 48 hours of receiving it. The staff will follow-up with patients who have not signed consent up to 3 times before clarifying whether the patient is still interested in the study. Participants may contact study staff at any time for a copy of the consent form for their records.

CLINICAL TRIAL

[For Recruitment and Screening Procedures, please see Section 4.0]

1. Once an individual completes the Part 1 and Part 2 (PHQ-9 item 9, DSM-5 Cross Cutting Symptom Inventory, DSI-SS, and any required follow-up items from the BDI-II) screening process and has determined to be eligible to participate in the study, Individuals will be automatically directed to the informed consent document for the study and given the opportunity to provide their informed eConsent. If two days after an eConsent form has been sent out, a participant has not provided informed consent or reached out to study staff, CBITs researchers will follow-up via phone, email, or text message

2. Once the consent form has been submitted, the staff will receive an electronic notification which will prompt him/her to confirm that the form was signed by the participant. If participants decline informed consent, their screener data will be retained for reporting purposes, but their screener information will not be used in future research unless they indicated willingness to be contacted for future research activities.

3. Once participants provide informed consent, staff will gather necessary information for payment processing including obtaining a signed W9 form an electronic signature service (e.g. DocuSign) if required by Northwestern University (depending on payment preference).

4. In parallel to requesting payment information, participants will enroll the participant in the text messaging system which will generate several introductory text messages to the participant's phone. Once a participant has (1) confirmed receipt of introductory messages and (2) completed baseline survey assessments, research staff will randomize the participant to a treatment arm. At the point of randomization, the participant will be considered enrolled.

5. REDCap reports will be generated daily to alert the study staff to follow-up with subjects who have not signed the digital consent form within 48 hours of receiving it. The staff will follow-up with patients who have not signed consent up to 3 times before clarifying whether the patient is still interested in the study. Participants may contact study staff at any time for a copy of the consent form for their records.

12.0 Waiver of Participant Signature on Consent Form:

Participant signatures will not be collected due to the distributed nature of participation. Instead, consent will be confirmed via REDCap survey by clicking an "Yes" button to the consent questions on the webform.

13.0 Waivers and Alterations of Consent Information:

N/A

14.0 Financial Compensation:

DESIGN STUDY

Longitudinal Usability Testing

Wave 1 (8-week intervention):
Participants will be compensated $20 for completing baseline measures and the initial set-up call, and $20 for each subsequent assessment point (Week 4 & 8), and $20 for each of the 2 interviews (Week 4 & 8). Amounting to a total potential earning of $100 per participant. Compensation will be offered in the form of an electronic Amazon gift card or check.

Wave 2 (4-week intervention):
Participants will be compensated $20 for completing the 4-week surveys, and $20 for completing the 4-week interview. Amounting to a total potential earning of $40 per participant. Compensation will be offered in the form of an electronic Amazon gift card or check.

CLINICAL TRIAL

We will reimburse all trial participants for completing research assessments. Participants will be compensated $25 per major assessment session (Baseline, Week 4, 8, 12, 16; we note that a subjective engagement questionnaire will be administered to those in the intervention group at week 1, but due to brevity this is not considered a major assessment point). Amounting to a total potential earning of $125 per participant. Compensation will be offered in the form of an electronic gift card or check.

15.0 Audio/Video Recording/Photography

DESIGN STUDY

Longitudinal Usability Testing

All interviews will be audio recorded. Subjects must consent to audio recording to be enrolled in the study. The audio recording will be transcribed before coding (see below).

Qualitative data will be analyzed using a six-phase thematic analysis as described by Braun and Clarke (2014). This six-step analytical approach facilitates the process of becoming familiar with the data, systematically identifying individual codes, grouping those codes into preliminary themes, defining and naming the final themes that commonly occurred across the entire data set, and then selecting examples from the data to accurately illustrate each theme. In thematic analysis, current theories or prior research can be used to identify critical concepts. These initial categories will be starting points for the data analysis.

Following IRB policy, data will be kept a minimum of 7 years after the completion of the study. Digital data gathered in the field will be uploaded to the Northwestern University servers.

CLINICAL TRIAL

All interviews will be audio recorded. Subjects must consent to audio recording to be enrolled in the study. The audio recording will be transcribed before coding.

Qualitative data will be analyzed using a six-phase thematic analysis as described by Braun and Clarke (2014). This six-step analytical approach facilitates the process of becoming familiar with the data, systematically identifying individual codes, grouping those codes into preliminary themes, defining and naming the final themes that commonly occurred across the entire data set, and then selecting examples from the data to accurately illustrate each theme. In thematic analysis, current

theories or prior research can be used to identify critical concepts. These initial categories will be starting points for the data analysis.

Following IRB policy, data will be kept a minimum of 7 years after the completion of the study. Digital data gathered in the field will be uploaded to the Northwestern University servers.

16.0 Potential Benefits of this Research:

DESIGN STUDIES
While there are no direct benefits to participants, participants may potentially derive some indirect benefit from being reflective about their own mental health self-management needs and desires.

CLINICAL TRIAL
There is no direct or immediate benefit to participants from whom data will be collected, although we anticipate some participants may receive support for their depression and anxiety through the intervention platform. The potential to future patients is that the study may provide fundamentally new and more effective low-intensity treatment approaches that would be more widely available.

The ultimate goal of this research is to develop an engaging DMHI that can effectively treat transdiagnostic psychological distress and associated psychological symptoms in an online manner is designed to meet the needs of young adult patients who are not interested in receiving face-to-face treatment. This DMHI will broaden the reach of mental health services available to the public by providing a service that is scalable and extends the reach of clinical services to users in an acceptable and tolerable medium. The risks associated with participating in the study are minor and are unlikely to cause more distress than standard available care. Conversely, the scientific and public health knowledge garnered from this study is likely to be considerable. Therefore, it is believed that the risks are reasonable in relation to the importance of knowledge to be gained.

17.0 Risks to Participants:

DESIGN STUDY and CLINICAL TRIAL

Risks

The proposed study poses minimal risks. All potential risks associated with participation in this study will be disclosed in consent documents. Any potential risks that might exist fall into four categories: (a) risks associated with the intervention; (b) risks associated with research assessments, consisting of questions about depression, anxiety, and personal functioning, and other mental and emotional problems; (c) risks associated with potential loss of confidentiality; and (d) risks of worsening mental or emotional state. We address each in turn below.

Risks of the intervention: DMHI programs generally have not been shown to cause any harm.[68]

***Risks associated with research assessments*:** Research assessments include questions about depression, anxiety, and other mental and emotional problems. Participants will give voluntary responses to self-report questionnaires and interview questions; they are told that they can decline to answer any questions that they choose. The instruments and methodologies are well tested and are not known to cause problems or distress on the part of the participants. All research interview-based assessments are audio-recorded, for the purpose of review to ensure quality assurance ratings of assessment performance, including ensuring that participants are comfortable with the interview procedures. Audio recordings will be maintained on a secure server with no identifying information in the labels for the duration of the funded study, unless other arrangements are made. On occasion participants may request that audio files be deleted before the end of the study, in which case we will comply.

Risks associated with potential loss of confidentiality: There is a slight risk of loss of confidentiality. There is some possibility that others may see the participant's messages. There is also a small possibility that databases may be hacked, even though they are behind secure firewalls. Measures to protect security in these instances are described below. Confidentiality may be broken by research staff to ensure the participant's safety if there is an imminent threat to self or others. There is also the remote possibility that research records will be subpoenaed by a court of law. All of these potential losses of confidentiality will be disclosed in the consent documents.

Risks of worsening mental or emotional state and or self-harm thoughts/events: Some participants may show a worsening of depressive or anxious symptoms, suicidality or problems during the study period. The development of suicidal ideation during the study remains the most serious risk. However, these are risks inherent in the population and would occur whether or not they were enrolled in the study. It is not believed that the risk of these depressive, anxious, suicidal, or other adverse outcomes are increased as a function of being enrolled in this study. All potential risks associated with participation in this study will be disclosed in consent documents.

This study imposes no restrictions on the participant in terms the use of other treatments.

Protections Against Risk

Protection for risks associated with potential loss of confidentiality: Identifiable data for all participants will be kept strictly confidential, except as mandated by law. Identifiable data from interactions with the text messaging platform will be maintained on FSM research servers and managed by our software developer, Audacious Software. Audacious Software (who developed the Simple SMS texting service used in this study). They will also maintain logs of all messages sent from and to the automated text messaging Simple SMS texting service is fully automated and is administered via Twillio and/or Azure.

The Simple SMS Application will operate on Feinberg servers. The Simple SMS application sends automated, personalized messages to users. To adapt messaging in real-time to user needs and preferences, the Simple SMS Application uses a machine learning engine running on secure Azure servers managed by the University of Toronto, that incorporates past and current users' de-identified data to inform content delivery. Accordingly, the Simple SMS Application will also make periodic API calls to the machine learning engine. Data sent by Simple SMS and received by the Toronto machine learning engine includes:

- users' randomly-generated study identifier
- content ratings (e.g., 1-5 ratings of interactions)
- engagement rates (e.g., whether or not the user responded to the interaction)
- contextual variables including de-identified demographic data (e.g., gender, age, K10 score), and preference data such as time of day, the number of days the user has been on study, strategies that a user is most interested in seeing or least interested in seeing

The output of the Toronto machine learning engine will inform the rate at which possible content types should be delivered to users in order to maximize engagement (e.g., reflection questions should be sent 75% of the time, and prompts 25% of the time).

Data related to the text message service (e.g., logs of messages sent and received) will be downloaded regularly during the study and stored on FSM research servers for analysis.

All other research files are kept on secure, password protected servers managed by Northwestern University Feinberg School of Medicine Information Technology. All electronic data will be stored on secure servers behind firewalls meeting all security requirements of the medical school. Any paper documentation (which we do not anticipate) is kept in locked file

cabinets or a locked file room. Participants will be assigned a numerical code for identification in the files. Names and other identifiers will be kept in separate password protected files. Audio and video data will be stored on secure servers.

Protection for risks of worsening mental or emotional state and/or suicidal thoughts/events: No study procedures are known to aggravate the risk of self-harm or suicide or depression, but we have nevertheless developed procedures to ensure safety of participants. Some participants may show a worsening of depressive symptoms, suicidality or problems during the study period. The development or worsening of suicidal ideation during the study remains the most serious risk. Participant care will always take precedence over study protocol.

There are a number of pathways through which suicidal risk can be detected. Suicidality may be detected through automated assessments at screening, baseline, and follow-up timepoints, through direct communications with the study staff during interviews, or through disclosure on the the text messaging system. In each of these instances, the goal will be to rapidly acquire additional information that can trigger safety procedures, if necessary.

Suicidality is assessed by self-report using item #9 of the PHQ-9, item #11 of the DSM-5 Cross Cutting Symptom Inventory, and the DSI-SS. If participants score >=1 on the PHQ-9 item 9 or item 11 of the DSM-5 Cross Cutting Symptom Inventory, or if participants score >=2 on the DSI-SS the REDCap questionnaire will branch to suicide item (item 9) from Beck Depression Inventory (2nd edition). If item 9 of the Beck Depression Inventory is 2 or 3 or if either items B or D on the DSI-SS >=3, a message will be displayed in the REDCap questionnaire making participant aware we are not an emergency service and should they need immediate help or be in danger, they should call or text the national suicide prevention lifeline, the Trevor Lifeline, text the Crisis Text Line. If item 9 of the Beck Depression Inventory is 2 or 3 or if either items B or D on the DSI-SS >=3 research staff will contact the participant for additional risk assessment and follow the CBITs Suicide Risk Assessment protocol detailed below. Additionally, if any suicide item (item 11 of the DSM-5 Cross Cutting Symptom Inventory, DSI-SS, PHQ-9 item 9, or BDI-II item 9) is endorsed (>0), we will also display crisis resources such as the national suicide prevention lifeline, the Trevor lifeline, the Crisis Text Line all of which are staffed 24/7 every day. We will also display a repository of warmlines that individuals can use.

Participants may also send free-text messages to the automated SMS system or coach, and these messages could indicate risk. We have developed a set of keyword rules, based on prior trials that could indicate risk (e.g. kill + self, end it, bridge, etc.). The automated SMS system will provide an immediate response to these that will include a list of 24-hour resources for immediate support (e.g. the Suicide Hotline, Crisis Text Line). The triggering message and surrounding transcript (to provide context), will be automatically forwarded to the study staff and the CBITs Clinical Monitor (a doctorate-level clinical psychologist or Masters-level clinical social worker) for review to determine if outreach is required.

Participants in the study may also send a message to a study staff at any point in the study and for any reason. In these instances, if staff receive a direct communication from a participant revealing suicide risk, they will enact the CBITs Suicidality Protocol which involves outreach to the participant for risk assessment via the Columbia Suicide Severity Rating Scale and management (including delivery of a coping plan, referral to resources, or contact emergency services in cases of imminent danger).

Ensuring participant safety: Once the study staff is notified of potential suicidality, the clinical monitor (a doctorate-level clinical psychologist or masters-level clinical social worker) will ensure all actions necessary are taken to ensure participant safety. A trained member of the research team will respond within one business day by evaluating all necessary data including study records, calling the participant to enact the assessment procedures based on the Columbia Suicide Severity Rating Scale and management procedures that include,

creating a support plan with the participant which is a recommended best practice when working with individuals experiencing suicidal ideation[69–71]. If necessary, trained study staff may call crisis services with the participant to complete a warm-handoff to crisis workers. In some rare cases study staff may refer patients to emergency services or request that a a "health and safety" check be performed. The study staff, in collaboration with the clinical monitor, will take any other actions deemed necessary to ensure the safety of the participant. Participants with significant suicidality that is not emergent will be provided with crisis resources (e.g. a safety plan, the national suicide prevention lifeline, the Trevor lifeline, the Crisis Text Line, and a list of warmlines). The monitoring clinician may also have the participant referred for more appropriate care.

Because RAs are usually the main point of contact for participants, they will be given thorough training in the assessment of suicidality. While the clinical monitors will be responsible for the management of suicidal participants, it is possible that an emergent situation will arise that requires immediate attention. RAs will be trained in the identification of imminent danger and procedures to ensure participant safety, including identification of the participant's location and contacting crisis services.

The PI will also be notified of all cases of imminent suicidality, will consult with the clinical monitor, and will be continuously updated. Any psychiatric problem rising to the level of an adverse event will be reported to the IRB and to the DSMB chair.

We note that risks related to suicidal thoughts and behaviors are inherent in the population and would occur whether or not they were enrolled in the study. We do not believe that the risk of these depressive, suicidal, or other adverse outcomes are increased as a function of being enrolled in this study or receiving our DMHI during the trial phases.

Deterioration in the severity of depressive or psychiatric symptoms is the other potential risk: If the RA believes that a participant has deteriorated substantially either by showing a substantial worsening in the presenting psychiatric symptoms or by the development of new psychiatric or treatment related symptoms, the clinical monitor will immediately be informed. The clinical monitor will evaluate the participant, notify the PI (and the DSMB once the CLINICAL TRIAL begins), and make any necessary referrals for the care of the participant. If the PI, (once the CLINICAL TRIAL begins, in consultation with the DSMB), determines it is in the participant's best interest to cease participation in the study, the participant will be terminated from the study, and referrals and assistance will be given in obtaining appropriate treatment. Reports will be filed with all necessary governing bodies, including the Northwestern University IRB (and the DSMB, once the CLINICAL TRIAL begins).

We note that these are risks inherent in the population and would occur whether or not they were enrolled in the study. We do not believe that the risk of these depressive, suicidal, or other adverse outcomes are increased as a function of being enrolled in this study. All potential risks associated with participation in this study will be disclosed in consent documents.

18.0 Provisions to Protect Participant Privacy and Data Confidentiality:

DESIGN STUDY & CLINICAL TRIAL

All screener and survey data will be electronically recorded and stored in Research Electronic Data Capture (REDCap) tools hosted at Northwestern University. REDCap is a secure, Web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Data communication between data entry computers and database servers will be encrypted via a

VPN client. Access to the VPN connection will require user authentication via username and password. Firewall software will restrict communication to the database server that is absolutely critical for conducting research. The databases and all data entry procedures will be designed to maintain the confidentiality of patients enrolled into the study. Numbers will be used to identify all written study materials, and no personal identifiers will be on such materials. All data collected via the REDCap assessments are transmitted using Transport Layer Security (TLS) encryption to prevent eavesdropping and tampering information while it is in the transmission pipeline.

While recruitment decisions are being made, screening data will be stored on Northwestern University servers that are encrypted. For those individuals who are not included in the study, their data will be retained for reporting purposes, but their data will not be used in future research. Screener information may be used to re-contact individuals who completed screeners to see if they would like to opt in to learning about additional research opportunities associated with this project. For those selected, their screening data will become part of the main research data, which will be stored and protected as discussed elsewhere in this protocol. Email addresses and phone numbers of participants will remain stored in an encrypted and protected database on Northwestern University's servers.

All audio recordings will be transcribed using GMR Transcription. GMR Transcription services maintains a proprietary web-based application for secure file management between the end customer, administrative staff, and transcriptionists. GMR Transcription's system is hosted using secure and redundant servers that feature the highest level of secure SSL encryption for all non-public site areas. Following delivery of transcript to NU's research team, GMR Transcription deletes all voice files from its servers. GMR Transcription's security procedures are detailed here: https://www.gmrtranscription.com/data-security.aspx

All text message interactions will be administered through software developed by Audacious Software. The text messaging architecture is built using the secure open source Simple SMS Messaging (SSM) platform. The SSM platform uses secure encryption technology when sending and receiving text message data. The SSM platform automatically encrypts participants' telephone numbers and any data sent and received using the SSM platform. Participant telephone numbers will be used exclusively for the purpose of administering text messages associated with this research study and for outreach in the event that research staff is required to contact participants. Telephone numbers are stored encrypted alongside other participant settings, including enrollment questionnaire responses, which are also encrypted when not in use. The SSM platform will collect logs of all messages sent and received from and to the automated text messaging service and that log, as well as all other data will be maintained and stored securely on local FSM servers that Audacious Software will maintain and manage during the study. Any de-identified variables and usage logs used for machine learning as noted in Section 17.0 will have all identifiers automatically stripped prior to transmission to University of Toronto servers. All data will be encrypted during transmission.

Data for all participants will be kept strictly confidential, except as mandated by law. Data from interactions with the text messaging platform as well as all other research files are kept on secure, password protected servers managed by Feinberg School of Medicine Information Technology. All electronic data will be stored on secure servers behind firewalls meeting all security requirements of the medical school. Any paper documentation (which we do not anticipate) is kept in locked file cabinets or a locked file room. Participants will be assigned a numerical code for identification in the files. Names and other identifiers will be kept in separate files. Audio and video data will be stored on secure servers and will only be available for coding by study staff.

To reduce the risk of loss of confidentiality through the participant's device, we will instruct patient participants on how to add a PIN to their phone to prevent unwanted access. We will clearly inform the patient participants of the risk of data insecurity.

19.0 Data Monitoring Plan to Ensure the Safety of Participants:

DESIGN STUDY

Should suicidality arise during a design interview, interviewers will be trained to respond using CBITs suicidality protocol.

In order to ensure the continued safety of participants during recruitment and execution of the elicitation workshops, we will carry out a daily data monitoring procedure (during business days). During which time an RA will review all incoming text messages from participants to ensure automatic safety key-word flagging is functioning properly. The RA will monitor incoming messages for disclosures of suicide or homicide risk.

If the RA identifies a message that reveals imminent threats to oneself or others (e.g., suicide plan and intent to die) the RA will notify the clinical monitor to to review the message, and if deemed necessary, research staff will follow the CBITs suicidality protocol and enact it via telephone (see attached **CBITs Suicide Risk Assessment (SRA**) within one business day.

Oversight of the trial is provided by the PI Dr. Meyerhoff. The RA or Research Manager will ensure that informed consent is obtained prior to engaging in research activities, and that the study is conducted according to the IRB-approved research plan.

Study data are accessible at all times for the PIs, the biostatistician, and all relevant Co-Is to review. The biostatistical team and study manager will conduct analyses of accrual, drop-outs, protocol deviations on a monthly basis initially, which may drop to quarterly once we are confident that procedures are functioning adequately.

CLINICAL TRIAL

Should suicidality arise during an interview, interviewers will be trained to respond using CBITs suicidality protocol.

In order to ensure the continued safety of participants during the study, self-report data will be reviewed daily (during business days) for new surveys that require follow-up and outreach using the CBITs Suicide Risk Assessment procedure as described in Sec. 17.0. An RA and behavioral Coach will review all incoming text messages from participants to ensure automatic safety key-word flagging is functioning properly. The RA will monitor incoming messages for disclosures of suicide or homicide risk.

If the RA or Coach identifies a message that reveals imminent threats to oneself or others (e.g., suicide plan and intent to die) the RA will notify the PI and clinical monitor to review the message, and if deemed necessary, research staff will follow the CBITs suicidality protocol and enact it via telephone (see attached **CBITs Suicide Risk Assessment (SRA**) within one business day.

Oversight of the trial is provided by the PI Dr. Meyerhoff. The RA or Research Manager will ensure that informed consent is obtained prior to engaging in research activities, and that the study is conducted according to the IRB-approved research plan.

Study data are accessible at all times for the PIs, the biostatistician, and all relevant Co-Is to review. The biostatistical team and study manager will conduct analyses of accrual, drop-outs, protocol deviations on a monthly basis initially, which may drop to quarterly once we are confident that procedures are functioning adequately.

The study will have a Data Safety Monitoring Board (DSMB), chaired by Greg Simon, MD (University of Washington and Kaiser Permanante, Seattle). Dr. Simon is a well-respected

mental health researcher. As chair of the DSMB, Dr. Simon will appoint additional board members as needed and will determine the meeting schedule. That said, we expect that the DSMB will meet twice in the first year of the trial (year 2 of the grant), and once in the final year. Drs. Mohr and Meyerhoff will attend the DSMB meetings as a non-voting member to facilitate communication between the DSMB and study personnel.

Dr. Meyerhoff will review adverse events (AEs) and serious adverse events (SAEs) individually in real-time and in aggregate at each DSMB meeting. The PI ensures all protocol deviations, AEs, and SAEs are reported to the IRB and the NIMH program officer according to the applicable regulatory requirements.

For this study, the following standard AE definitions are used:

Adverse event: Any unfavorable and unintended sign or symptom temporally associated with the use of digital mental health interventions, regardless of whether it is considered related to intervention.

Serious Adverse Event: Any AE that results in any of the following outcomes:

- Death
- Life-threatening situation
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs are graded according to the following scale:

- Mild: An experience that is transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities.
- Moderate: An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities.
- Severe: An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale:

- Not related: The AE is clearly not related to the study procedures (i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
- Possibly related: An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
- Related: The AE is clearly related to the study procedures.

SAEs and specific treatment-associated AEs are reported to the IRB and NIMH program officer within 24 hours.

20.0 Long-term Data and Specimen Storage and Sharing:

De-identified study data will be made available to scholars upon request. A data use agreement will be executed before study data is released to a researcher or organization that is not part of the study team. The data use agreement will specify what data will be transferred to another organization or research center. Some journals now require that data used in publications must be provided to the journal and may be made public. In those instances, we will provide a de-identified dataset to the journal. Study consent forms will explain the range of information that may be shared with collaborators.

Only the PI and research team members listed below will have full access to identifiable data. Data will be kept for a minimum of 7 years after the end of study date.

For the CLINICAL TRIAL data:

De-identified quantitative data will be shared through the NIMH Data Archive, as described below:

Data Sharing Plan
All data will be made free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects.

Where will the data be available. Data will be deposited into the National Database for Clinical Trials Related to Mental Illness (http://ndct.nimh.nih.gov, NDCT), which is a part of the NIMH Data Archive (NDA). The NDA provides an infrastructure for data collection, retrieval, and resulting reporting using a single Oracle database that has three different web sites that serve as front ends for different research communities.

Who will have access to the data. The NDA follows NIH's data access principles. The NDA provides basic demographic and aggregate summary information for general public use. Such summary information may include summary counts and general statistics on completed assessment instruments. Access to subject level datasets submitted and stored in the NDA will only be provided for research purposes through the completion of the NDA Data Use Certification.

What data will be shared. We will share descriptive data such as all assessments completed, demographic data. Additionally, we will submit all outcome measures from our trials. Submitted data will conform with relevant data and terminology standards.

When will the data be shared. Descriptive data will be submitted every six months. Analyzed datasets on study outcomes will be deposited in the repository as soon as possible but at least prior to any publication and associated with a study. Regardless of any publications, all data will be deposited no later than within none year of the completion of the funded project period for the parent award.

How will researchers locate and access the data. We will acknowledge the NDCT repository and the funding source in any publications and presentations. We will be using NDCT, which is an NIMH-funded repository, this repository has policies and procedures in place that will provide data access to qualified researchers, fully consistent with NIH data sharing policies and applicable laws and regulations.

21.0 Qualifications of Research Team to Conduct the Research:

The Center for Behavioral Intervention Technologies (CBITs) at NU conducts research to design and evaluate behavioral intervention technologies and technology enabled services.

David Mohr, PhD is the director of CBITs within Feinberg School of Medicine and Co-Director of NIMH Multidisciplinary Training Program in Digital Mental Health. He has vast experience conducting mental health research at the intersection of behavioral science, technology, and clinical intervention. Dr. Mohr is a licensed clinical psychologist in the state of Illinois and will provide primary supervision for suicide risk assessments.

Jonah Meyerhoff, PhD is a Research Assistant Professor in the Department of Preventive Medicine and a member of the Center for Behavioral Intervention Technologies where he has experience

executing clinical trials, and overseeing the development, training, and monitoring of service protocols for technology-enabled services. He has experience conducting clinical research in the digital mental health domain. Dr. Meyerhoff is a PhD level clinical psychologist and is licensed in the state of Illinois.

Mary Kwasny, PhD is an Associate Professor in the Department of Preventive Medicine, Division of Biostatistics at Northwestern University Feinberg School of Medicine. Dr. Kwasny will be responsible for overseeing all statistical analysis functions of the project. Dr. Kwasny has over 16 years of experience as a collaborative biostatistician, and has held several leadership roles both at Northwestern University's Programs in Public Health, as well as the American Statistical Association professional society. She is currently the statistician for the Center for Behavioral Intervention Technologies.

Rachel Kornfield, PhD, is a research assistant professor in the Department of Preventive Medicine. She has several years of experience conducting interviews related to mental health and health services delivery. She is a member of the People, Information, and Technology Changing Health (PITCH) Lab and the Center for Behavioral Intervention Technologies (CBITs).

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