Technology Enabled Services to Enhance Depression Care

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fPROTOCOL TITLE: Technology Enabled Services to Enhance Depression Care

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STUDY SUMMARY:

Investigational Agent(s) (Drugs or Devices)	The Vira Mental Health Measurement Platform (Vira) is a mobile application (app), secure clinician portal/website and administrator portal/dashboard.
IND / IDE / HDE #	Not Applicable.
Indicate Special Population(s)	☒ Children ☐ Children who are wards of the state ☐ Adults Unable to Consent ☐ Cognitively Impaired Adults ☐ Neonates of Uncertain Viability ☐ Pregnant Women ☐ Prisoners (or other detained/paroled individuals) ☐ Students/Rush Employees
Sample Size	Clinical Trial: 130 Patients
Funding Source	National Institutes of Health
Indicate the type of consent to be obtained	☒ Written- eConsent ☐ Verbal/Waiver of Documentation of Informed Consent ☒ Waiver of HIPAA Authorization ☒ Waiver/Alteration of Consent Process
Site	☐ Lead Site (For A Multiple Site Research Study) ☐ Data Coordinating Center (DCC)
Research Related Radiation Exposure	☐ Yes ☒ No
DSMB / DMC / IDMC	☒ Yes

	☐No

OBJECTIVES

Depression and anxiety are common[1] and impose a tremendous societal burden in terms of cost, morbidity, quality of life, and mortality.[2-5] Yet, few people are able to obtain adequate or appropriate treatment.[6,7] While 100s of trials have demonstrated the efficacy of technology-enabled services (TESs) in reducing depression and anxiety,[8-13] the many attempts to implement these validated programs into large value-based care systems have failed.[14-18] Patients do not engage with the technologies, they stop answering reminder calls from staff, and TESs do not fit into clinician workflows.

The overarching goal of this research project (RP) is to design, develop, and evaluate a TES that can be successfully implemented to support the treatment and management of depression and/or anxiety in primary care/family medicine clinics. The design innovation focus of this RP will be the use of mobile phone sensor data to identify behaviors, psychological states, and environmental conditions in real time[19] to support patients' behavior change. An intelligent patient-facing app will be designed and evaluated, which passively acquires behavioral markers and automates prompts to the patient, thereby eliminating much of the effort required by users to engage with mental health apps. Our software collaborators at Ksana Health have developed algorithms that can identify mobility patterns, physical activity, and other behavioral targets that can be sensed. While technological capability to track behaviors is increasing, the field does not yet understand how to use these technologies to promote behavior change for the treatment of depression.[14] We will design interfaces that make it easy for patients to understand and act on sensed information for managing depression. By reducing the need for patients to manually enter information into an app, the value/burden ratio is significantly increased. These tools will be designed to be used in short bursts of 30-60 seconds, which is how most people interact with apps,[27,28] and which we have found promotes sustained engagement.[29] The intervention protocol will be based on principles of behavioral activation.

This patient app, called Vira (which is a product developed and managed by Ksana Health), will be evaluated with patients receiving care from Rush University Medical Center's primary care and family medicine clinics, which serve racially, ethnically, and economically diverse communities. The TES will include a service protocol that defines how a coach will interact with the patient around these sensed behavior targets, a coach dashboard that provides visibility into app use and patient status, and tools that enable coach communication with the patient to provide support. Thus, we will evaluate a TES that can support depression and/or anxiety care in general medicine, with a unique innovation focus on patient-facing features that harness emerging personal sensing methods to support behavior change in patients with depression. To achieve these goals, we have the following 3 aims:

Aim 1: Design Study (completed in years 1-2 of the project period): Design and develop a TES for patients receiving care in a primary care/family medicine setting that harnesses personal sensing technologies. A TES for depression has been designed, developed, and refined with input from key stakeholders including patients, staff, physicians, and others identified during the design process. User-centered design (UCD) principles were used to design the technology, service protocol (e.g., intervention and coordination protocols), and an implementation plan. Design efforts focused on the integration of personal sensing technologies.

Aim 2: Randomized Clinical Trial. Pilot the feasibility of an Optimization, Effectiveness, Implementation (OEI) Hybrid trial of the TES. The OEI Hybrid trial extends the hybrid (type 1)

effectiveness-implementation trial[30] design by allowing optimization of the TES technology, service protocol, and implementation plan to the delivery context.[31,32] The TES will be compared to a control treatment (CT) app that provides basic psychoeducation.

Sub-aim 2.1 Effectiveness. The primary outcomes are patients' depression severity (PHQ-9)[33], and anxiety severity (GAD-7)[34]. The secondary outcome is quality of life (PedsQl). Patient characteristics (race, ethnicity, income, age, health status, substance and alcohol use, other mental health treatment [including pharmacological]), stigma, discrimination, and mobile phone use will be examined as moderators.

Sub-aim 2.2 Implementation. Implementation targets will include reach (number eligible, treatment uptake, treatment completion) and cost.

Sub-aim 2.3 Optimization. We will use quality improvement methods[32] to continuously improve the technology, service protocol (e.g., intervention and coordination protocols), and implementation plan.

Aim 3. Experimental Therapeutics Aims. We hypothesize that the impact of core UCD targets (usability, usefulness, and satisfaction) in the TES will result in increased objective and subjective markers of engagement relative to the CT, with improved downstream effects on depression. We also hypothesize the moderating effects of patient characteristics on engagement and depression will be lower levels in the TES arm, relative to CT, as a result of inclusion of users' voices through the design and optimization processes.

This project will result in the first TES for depression that can be successfully implemented in primary care and family medicine clinics. It will be achieved by creating tools that fit into the fabric of patients' lives by harnessing personal sensing.

BACKGROUND

Primary care is the de facto setting for depression and anxiety treatment for the majority of people.[7,37-39] However, patient outcomes in primary care are extremely poor due to failure to identify symptoms, suboptimal treatment, and treatment access barriers.[40-42] Digital mental health strategies have been used to address depression and anxiety in primary care.

Technology-enabled services (TESs; which we define as a remotely delivered clinical service supported by digital tools and/or applications along with a human coach) offer the potential for adaptable psychological services that can be delivered more efficiently at scale that is not feasible for in-person services. Today, 81-85% of Americans own a smartphone, among whom 95% almost always have their phones with them.[47,48] Rates are similar across racial and ethnic groups.[49] RCTs consistently show that TESs, when coupled with low intensity coaching, are highly effective for depression.[50,51]

However, evidence is emerging that implementation efforts of TESs in real world healthcare systems have failed.[14,15,16-18] Patients do not use the technologies, and TESs do not fit into the workflow of staff and providers. Simply put, current generation TESs do not engage patients or providers. Patients become frustrated and stop answering reminder calls.[16,17]

We used our Accelerated Create-To-Sustainment (ACTS) research model to design and evaluate the technology, service protocols, and identify an implementation plan for a TES that is usable and useful, aimed at supporting patients receiving primary care from a provider at Rush University Medical Center. The distinct focus of this RP will be to design intelligence, an emerging property of digital technologies, into the TES, harnessing personal sensing.[52] Sensing is changing behavioral health. For example, automated step counting improves physical activity interventions by making measurement effortless.[53] There are many more behaviors relevant to depression and anxiety that until recently have required self-report. Methods of passive sensing

have emerged that can track behaviors related to depression continuously and effortlessly.[19]

Personal sensing uses data from sensors in common devices to estimate behaviors, psychological states, and environmental conditions.[19] Using the increasingly large complement of sensors embedded in mobile phones, researchers have been able to accurately estimate mobility, physical activity, the location types a person visits, sleep duration and circadian rhythm, online social activity, and medication adherence.[19-26] While our technological capability to track behaviors is increasing, we have yet to understand how to use this capacity to intervene with patients. Roughly half of Americans have low graphic literacy, creating challenges in the design of patient-centered communication tools.[54] In addition, the ability to continuously track behaviors opens new intervention opportunities, requiring service design.[14] Thus, a primary and unique focus of this RP within the Chicago ALACRITY Center will be to design a TES that harnesses emerging personal sensing methods to support behavior change in patients with depression.

RANDOMIZED CONTROLLED TRIAL (RCT) STUDY INTERVENTION(S) / INVESTIGATIONAL AGENT(S)

Participants enrolled in the Randomized Controlled Trial (RCT) will be assigned to receive one of two study interventions: (1) Technology Enabled Service (TES), or (2) Control Treatment (CT). The design of the TES and CT interventions were determined through the design study and negotiations with our software development partners (Ksana Health and Audacious Software).

Technology Enabled Service (TES)

The TES consists of digital technologies that connect patients to a coach remotely, providing tools for monitoring patient symptoms, communication, and delivery of tools and psychoeducation that support self-management strategies. Patients randomized to the technology enabled service (TES) condition will use Ksana Health's "Vira" Mental Health Measurement Platform with support from a study coach. Vira by Ksana Health delivers passive and continuous remote patient monitoring + digital therapeutics for behavioral health. Vira uses smartphones as a passive sensing device, requiring no special equipment or additional costs for users who already use a smartphone. The app uses passive sensing technology to identify activities and behaviors that appear predictive of a users' enjoyment and accomplishment, displays those activities to the user, and prompts participants to reflect on how to increase their sense of enjoyment and their sense of accomplishment. Additionally, the app will contain psychoeducational resources to help participants self-manage symptoms of depression and anxiety. Coaches will have the benefit of receiving objective patient data and insights, allowing them to monitor app usage and provide remote support. Northwestern University study team member(s) will be trained to deliver the digital mental health coaching intervention to support study participants in using Vira. The coach will help participants with app engagement, knowledge, fit, and implementation of self-management strategies. The coach will also provide behavioral activation-informed content to participants via messaging. Content will be in the form of previously established peer-led delivery models. To supplement telephone communication between study coaches and participants, we have contracted with Audacious Software to develop a secure text messaging platform to facilitate delivery of the coaching service. All text messaging data will be stored on Northwestern University Feinberg School of Medicine's on-premises servers. The TES will be delivered over a period of 8 weeks.

Control Treatment (CT)

Participants randomized to the CT condition will use an app designed by researchers at the University of Virginia to deliver psychoeducational content to help people self-manage symptoms of stress, depression and anxiety. The mood education app will be cloned by Audacious Software for use in this study and data will be hosted on Northwestern University Feinberg School of Medicine's AWS environment.

RCT PROCEDURES INVOLVED

We will utilize an RCT based on our OEI hybrid trial design. A total of 130 Rush Patients will be randomized to either TES or Control Treatment (CT). Depressive and anxiety symptoms and other outcomes will be measured at baseline, 4, 8, and 12 weeks. Beyond 12 weeks, participants will be allowed to continue use of the apps for the study duration, though the TES coaching service will be discontinued at the end of 8 weeks. App use will be tracked for the entire study duration. Should a patient begin treatment but stop engaging, a single question survey will be administered to gauge the reason why and potentially optimize treatment as a result of the feedback.

Patient populations will be all Rush patients who are 13+ years old who are experiencing at least moderate symptoms of anxiety and/or depression and are open to using a smartphone app to get mental health support. Out of the total number of participants, 10%, or approximately 13 patients are expected to be adolescents.

All participant management will be performed by personnel at Northwestern University, and Rush.

Assessment Strategy for Sub-aim 2.1 Effectiveness

The primary outcomes are depressive symptom severity, measured using the PHQ-9[33], and anxiety symptom severity, measured by the GAD-7. Administration will occur as part of the research protocol via REDCap online, or if not feasible via phone.[101] Secondary outcomes include quality of life. Primary and secondary outcome data will be gathered from patients as outlined in Table 1 below.

Table. 1: Primary and Secondary Outcome Measures

Outcome/Construct	Measure	Method	Timing	Type
Depressive symptoms	PHQ-9	Self-report Survey	0w, 4w, 8w, 12w	Primary
Anxiety symptoms	GAD-7	Self-report Survey	0w, 4w, 8w, 12w	Primary
Quality of Life	PedsQL	Self-report Survey	0w, 4w, 8w, 12w	Secondary

Additional data will be collected to evaluate intervention use, usability, satisfaction, and engagement. Measures of discrimination and stigma will be administered. Patient self-report measures have been uploaded to the eirb+ system for review. See data collection packets containing the measures to be administered via REDCap at screening, baseline, week 4, week 8, and week 12.

Assessment Strategy for Sub-aim 2.2 Implementation

Reach will be measured as follows: 1) Number of eligible patients will be the number of patients with PHQ-9≥10 at a clinic visit during the study recruitment period; Treatment uptake will be the number of patients consented and randomized; 3) Treatment completion will be the number of patients completing at least 6 weeks of the 8-week treatment.

Optional Usability/User-Feedback Interviews (4w, 6w, 8w)
Participants will be informed during the informed consent process that they may be invited to complete optional interviews. All interviews will be conducted by telephone. At the end of the week 4 self-report survey, participants will be asked if they would like to provide additional feedback about their experience using the Vira app and working with the study coach via paid interviews. Participants who express interest in providing feedback will be contacted by study staff to schedule the optional interview session(s). More information about the nature and timing of the optional interviews is provided below.

Vira app usability interviews (4w, 6w, 8w)
As we begin enrolling the clinical trial, we will invite the first participants randomized to the TES condition to provide feedback on the usefulness and usability of the Vira application. These optional interviews will be administered to approximately 10 participants.
The app usability interview guide has been uploaded to the eirb+ portal for review.

Coaching user feedback interviews (4w)
All participants randomized to the TES will be invited to share additional user feedback about their experience working with the study coach at the week 4 (mid-treatment) timepoint.
The coaching user feedback interview guide has been uploaded to the eirb+ portal for review.

Failure to Initiate Treatment
If a participant fails to initiate treatment or fails to continue with treatment but is still engaged with the study, a single question survey will be administered to gauge the reason why they decided to not engage with the treatment.

Optional Focus Group (Post-Trial)
Approximately 12 participants will be invited to participate in a one-time, virtual focus group after completion of the trial to share their feedback on their participation (reasons for enrolling, for remaining/not remaining engaged, etc.) as well as their thoughts on how to best disseminate study findings to study participants.

Participants will be invited via email to participate in this add-on study activity. Participants will be instructed to express interest by replying to the email. Participants will also be informed that space is limited. Once the participant expresses interest, the study team will assess number of spaces available and other demographic information (to ensure a range of representation) and reply with either:

- A link to the addendum document which outlines the focus group details (objectives, benefits/risks, and confidentiality), followed by a brief form to provide their availability. The addendum and the availability form are hosted on Northwestern's instance of REDCap, or
- A message to thank participant for their interest and to let them know spaces have been filled.

Adolescents 13-17 years old will require parental consent to participate in the focus group. Participants who sign the addendum document will be scheduled for a focus group according to their availability.

Due to the low-risk nature of the focus group and the fact that participants are being invited after having completed all other study activities, we will use an addendum document (versus a revised study consent form). An addendum will decrease the participant burden and potential

confusion of re-reading the entire consent form when they have already completed all other study activities.

These virtual focus groups will be audio-recorded and transcribed. Transcripts will not contain identifiers. This is detailed in the addendum document.

Risks are described in the “Risks” and “Protection Against Risks” sections of this document. Risks are explained in the addendum document,

The addendum document will not be translated into Spanish as the study sample contains no adolescents with Spanish-speaking parents.

DATA AND SPECIMEN BANKING
Deidentified data will be stored indefinitely for secondary analyses.

STUDY TIMELINES
RCT Enrollment Timeline
This trial will utilize a rolling recruitment strategy with patient-level randomization. Recruitment will begin in the third year of the grant-funded project and continue into year four.

RCT Timeline of Participant Activities
Active participation will last 12 weeks for each study participant. Participants will use the study apps and receive coaching (group 1 only) for the first 8 weeks. We will unobtrusively track all communication with the study coach. Assessment will continue through week 12. Study assessment milestones are laid out in tables 3 and 4 below.

Table 2. Online surveys to be administered to all participants

Method	Week 0	Week 4 Mid-Treatment	Week 8 End of Treatment	Week 12 Post-Treatment
Self-report Survey	x	x	x	x
App Usage	Continuous, unobtrusive			

Table 3. Optional interview data to be collected from patients randomized to TES

Method	Week 4 Mid-Treatment	Week 6	Week 8 End of Treatment
Vira app usability interview	X	X	x
Coaching user-feedback interview	X		

Table 4. Optional focus group be completed with patients randomized to control and TES

Method	Post-Trial Completion
Focus Group (semi-structured interview guide)	X

The anticipated completion date for primary analyses is March 31st, 2024.

RCT INCLUSION AND EXCLUSION CRITERIA:
Trial participation will be offered to patients at Rush University Medical Center aged 13 or older. Children under the age of 13 will be excluded given likely differences in development and

smartphone ownership that would make such young children an inappropriate population for evaluating the technology enabled service and implementation plan.

Inclusion Criteria: US Citizen/Resident (for payment purposes) living in the US during the 12-week study period (for tech functionality, data security, and safety management purposes), 13 years or older (if age 13-17, parent/caregiver must provide consent, a consent process is in place for English-speaking minors with Spanish-speaking parents), English speaking, eligible to receive care through Rush University Medical Center or its clinical affiliates, owns an Android or iPhone smartphone with an up-to-date operating system, has used a smartphone in the last 7 days, at least moderate symptoms of depression (PHQ-9 greater than or equal to 10) and/or anxiety (GAD-7 greater than or equal to 8)
Exclusion Criteria: Severe suicidality (as defined by presence of a plan + intent to act on that plan)

VULNERABLE POPULATIONS
Adolescents (ages 13-17) meeting the previously described inclusion criteria will be eligible to participate. The proposed study poses minimal risks for adolescent participants. All potential risks associated with participation in this study will be disclosed in the combined assent and parental consent document. Potential risks are identical to those of potential adult participants (ages 18+) and fall into the four categories addressed later in this protocol: (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.

RCT RECRUITMENT METHODS
Patients will be recruited from Rush University Medical Center clinic-based sites, social media and other platforms, and through subject recruitment registries.

Clinic-based recruitment will occur at Rush University Medical Center primary care, family medicine, internal medicine, collaborative care, psychiatry clinics, community health clinics (e.g., school-based health centers), pediatrics, the Adolescent Family Center, and may be extended to other clinics as needed.

All patients judged as potentially meeting criteria for treatment by the care team and/or a member of the research team will be offered recruitment materials. Specifically, they will offer participation in the Trial to all patients aged 13 or older whom they deem appropriate via a flyer or an email/MyChart message with a description of the study and a link to complete the online eligibility screener. Information commonly used by providers to determine need for mental health care are routine screening with the PHQ-9, GAD-7, physician referral, and patient complaints and requests.

Recruitment will also take place using Rush's MyChart Recruitment feature on Epic. The research team will invite patients who have had a recent visit or have a visit scheduled to their Rush primary care doctor. After receiving IRB-approved recruitment materials, they will have the option to opt in or out of additional follow-up, including a link to complete the online eligibility screener. Patients who do not respond to the initial invitation may receive one additional invitation. Patients who express initial interest but do not read the team's follow-up message will receive a reminder. The team will know who has not read the MyChart message via the "un-read notification" feature.

Parents of minors who themselves receive care at Rush may also receive a flyer or an email inviting their child to take part in the study. The email scripts have been uploaded into the eirb+ system.

Patients may also receive a teaser advertisement the size of a business card with a QR code directing them to an online version of the full recruitment flyer. Patients will confirm their interest by initiating the online screening and consent procedure.

Specifically:

- Patients will be offered a flyer or sent an email/MyChart message with a description of the study and a link to complete the online eligibility screener.
- A flyer will be included with the PHQ-9 and GAD-7 clinic questionnaires. Patients will confirm their interest by initiating the online screening and consent procedure.
- The PHQ-9 and GAD-7 screeners will contain an add-on form inviting participants to provide their contact information if they're interested in being contacted about free resources, programs, or studies that may help manage their mental health. Rush personnel would follow up with interested patients to review main points from IRB approved recruitment flyer and direct them to the screener link. Rush personnel would not share contact information for patients who may not be interested.
- A member of the research team may approach patients in the waiting room to offer a flyer and those who express interest will be invited to visit/initiate the online screening either on the patient's personal device or a Rush-issued tablet.

Social Media and Other Platforms. Rush and Northwestern teams will post recruitment messages to their social media pages that direct participants to a link that includes an online version of the full recruitment flyer and to the online screening. These have been uploaded to the eirb+ system. Rush will also post the study to their Clinical Trials website which will include a description of the study and the study team's contact information.

Community-Based Recruitment

The Rush research team will disseminate study flyers at community events hosted by Rush and Rush's community partners (back-to-school fairs, resources fairs, wellness events, etc.). Event attendees will be informed that inclusion criteria include being a Rush patient. If attendees report that they are not currently a Rush patient, they will be encouraged to take the flyer in case they seek care at Rush at any point. Those who report being a Rush patient will be encouraged to scan the QR code to learn more about the study and complete a screener survey. Patients will confirm their interest by initiating the online screening and consent procedure.

The Rush Education and Career Hub (REACH) supports education through academic enrichment, mentoring, and internships by connecting with underrepresented students, their parents, educators, and staff to: spark and catalyze STEM learning in and outside the classroom, design solutions and address challenges in their communities and beyond, improve overall community health. Interested REACH-affiliated adolescents may receive a flyer or an email with a description of the study and a link to complete the online eligibility screener. We will use the currently approved study flyer and email invitation, only slightly tailored for this younger demographic. Patients will confirm their interest by initiating the online screening and consent procedure. The REACH team may also include recruitment materials in their social media or newsletter platforms.

Clinical trial recruitment advertising materials have been uploaded to the eirb+ system for review.

Subjects who do not provide the necessary information to determine eligibility via the online screener will be contacted by telephone to obtain the information needed to make an eligibility determination.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES
We will reimburse all RCT participants for completing research assessments.

All subjects can earn up to $100 for completing online study assessments. The reimbursement schedule for each completed assessment is outlined in table 6 below.

Table 5. Compensation for Completion of Online Surveys

Method	Week 0	Week 4	Week 8	Week 12
Self-report Survey	$25	$25	$25	$25

Subjects randomized to the TES arm can earn additional compensation if they are interested in completing additional optional user feedback interviews. Compensation for each additional interview completed is outlined in table 6 below.

Table 6. Compensation for Completion of Optional Interviews

Method	Week 4	Week 6	Week 8
App Usability Interview	$25	$25	$25
Coaching Feedback Interview	$25		

Table 7. Compensation for Completion of Optional Focus Group

Method	Post-Trial
Focus Group (semi-structured interview guide)	$25

Depending on Northwestern University payment guidelines and availability at the time of participation, payments to participants will be issued in one of the following ways:

- Gift card: The following gift card payment methods are available to participants earning no more than $225 per calendar year:
  - Amazon.com gift card: Participants will be sent a code via email that will allow them to redeem an Amazon.com gift card. Gift Cards may only be redeemed toward the purchase of eligible goods and services provided by Amazon.com. Participants must create an account with Amazon to use the card. No fees apply to Amazon Gift Cards and the balance will not expire.
  - PNC Stored Value (Visa) Card: If participants do not have an Amazon account or do not wish to be compensated through Amazon, they may request a Stored Value (Visa) Card instead. The cards may be virtual or physical as per participant preference.
- Check: Participants earning more than $225 per calendar year must be paid by check. Checks require a signed W9 form. The check may be mailed to the participant's address.

- Through Northwestern University (NU) Payroll if the participant is an NU employee

Participants will be informed that it will take approximately 2-4 weeks for payment to be processed.

WITHDRAWAL OF PARTICIPANTS
Patient participants can discontinue the TES and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons.
The reason(s) for discontinuation will be documented and may include:
Patient voluntarily withdraws from treatment (follow-up permitted);
Patient withdraws consent (termination of treatment and follow-up);
Patient is unable to comply with protocol requirements; (termination of treatment and follow-up);
Patient demonstrates disease progression (termination of treatment and follow-up unless continued treatment with study intervention is deemed appropriate at the discretion of the investigator);

RISKS TO PARTICIPANTS
Risks
During clinical trial described above, patient participants will be assessed using self-report measures over 3 months. Participants randomized to TES may be offered user feedback interviews to provide feedback on their experience using the Vira app and working with the study coach. 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: Digital mental health intervention programs generally have not been shown to cause any harm. The primary risk of the intervention is participants being distracted by their mobile phones while engaged in activities that demand their complete attention. Participants occasionally try to use mobile apps while driving motor vehicles, and therefore will be instructed never to use the mobile phone while driving. Participants will be made aware of the physical, financial, and legal risks associated with using the phone while driving. If the research team becomes aware of a participant engaging in this behavior, the PI and mentors will consult to determine the most appropriate way to eliminate this risk.

Risks associated with research assessments: Research assessments include questions about depression and other mental and emotional problems. Participants will give voluntary responses to interview questions; they are told that they can decline to answer any questions that they choose. The instruments and methodologies are well tested in adolescents (13-17 years) and adults (18+ years old) and are not known to cause problems or distress on the part of the participants. All research interview-based assessments are audio-recorded, or video recorded, for the purpose of review to ensure quality assurance ratings of assessment performance, including ensuring that patients are comfortable with the interview procedures. Audiotapes and videos 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 patients may request that audio files or videos 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. While transmissions from mobile phones or other devices are protected, and communication occurs within a secure messaging platform, there is some possibility that others may see the participant's smartphone or device. 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 patient'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. Given the nature of focus groups, there is risk of loss of confidentiality. All of these potential losses of confidentiality will be disclosed in the consent documents.

Risk of suicide: Some participants may show suicidality or problems during the study period, which is the most serious risk. This risk is 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 assent, parental consent, and adult consent documents.

Protections Against Risk

All patient participants will continue to receive all care through their providers within the Rush system. Thus, the full range of available treatment options are available to participants, including antidepressant medications, psychotherapy, electroconvulsive therapy, or inpatient treatment. The benefits of these alternatives are that they are evidence-based, more intensive and specialized.

Protection for risks associated with potential loss of confidentiality. Data for all participants will be kept strictly confidential, except as mandated by law. 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 and will only be available for coding by study staff. All intervention technologies will be developed using up-to-date security measures.

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. To protect against unauthorized access of patient participant intervention data on a mobile phone, intervention data will be encrypted on the phone itself and configured to self-destruct at the command of study staff (for example in the case a phone is reported missing). We will clearly inform the patient participants of the risk of data insecurity.

To reduce the risk of loss of confidentiality associated with the focus group, participants will be asked to log in with first names only; and the research staff will rename anyone who uses both first and last names. Participants will also be asked to refrain from sharing the content of the discussion with anyone outside of the group.

Protection for risk of suicidality: The development of suicidal ideation during the study remains the most serious risk. Patient care will always take precedence over study protocol.

There are a number of pathways through which suicidal risk can be detected. During the trial phases, suicidality may be detected through automated PHQ-9 self-report assessments, through direct communications with the study coach via phone or messaging (email, text, etc.) or through direct communication with research staff during user feedback interviews. In each of these instances, the goal will be to rapidly acquire additional information that can trigger safety procedures if necessary.

Suicidality will be monitored through weekly assessments. Participants who rate Question 9 of the Patient Health Questionnaire-9 (i.e., “Over the last 2 weeks, how often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way”) a 1 or higher will receive a second item from the Beck Depression Inventory (2nd ed.) that is more specific in identifying suicidal intent, asking participants who indicate that they would like to kill themselves, or would kill themselves if they had the chance will be considered to have “elevated suicidality.” For participants with “elevated suicidality,” a crisis message is displayed to the participant (see message verbiage below) and an alert is sent to the research team and a trained member of the research team will respond within two business days by calling the patient to enact the assessment procedures based on the Columbia Suicide Severity Rating Scale and management procedures that follow clinical guidelines described below.

Crisis Message Displayed to Participants in REDCap:

This research study is NOT an emergency or crisis service.

If you are experiencing a life-threatening emergency such as serious thoughts or plans to end your own life or the life of anyone else, please call or text the numbers 9-8-8 to reach the Suicide and Crisis Lifeline.

If you're looking for crisis supports who specialize in serving members of the LGBTQIA+ youth communities, please call the Trevor Project at 1-866-488-7386 or text "START" to 678-678

For non-crisis support, warmlines are also available, find one here: http://www.mhanational.org/warmlines

When suicidality is expressed by the participant directly to the study coach in a phone call or text, the coach similarly follows up to conduct a risk assessment based on the Columbia Suicide Severity Rating Scale and engage the participant in risk management procedures based on their risk status.

Finally, participants may express suicidality during user feedback interviews with research study staff. While planned questions do not probe suicidality, participants may, in the course of the interviews, express suicidality, in which case they will be considered have “elevated suicidality” and trained research staff will conduct risk assessment and management procedures

Description of assessment procedures using the Columbia Suicide Severity Rating Scale
All participants with “elevated suicidality” will receive additional follow-up assessment using the Columbia Suicide Severity Rating Scale[1] to obtain further information on level of risk by the research staff member, who will be trained on its administration. Participants with elevated suicidality that is not emergent will be provided with a personalized coping plan that includes crisis resources (e.g. the 9-8-8 Suicide Hotline, Crisis Text Line), referred back to their physician, and their physician will be informed. In the case of a psychiatric emergency during

the trial phases (including imminent suicide risk), all necessary efforts will be made to ensure the safety of the participant, including a warm handoff to the National Suicide Prevention Lifeline, possible outreach to emergency services and informing the participant's physician of risk status and all risk management actions taken. All risk management activities will be supervised by the Center's clinical monitor, a PhD level clinical psychologist. A masters level social worker may supervise the suicidality assessments.

In the event that a suicidality assessment is completed with an adolescent participant (age 13-17), a parent or guardian will be notified that a risk assessment was completed with their child. Limits to confidentiality have been specified in the adolescent consent/parental consent document.

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 or receiving TES during the trial phases. All potential risks associated with participation in this study will be disclosed in consent documents.

Protection for Spanish-speaking parents of minors
The study team will use Spanish-language materials that have been translated and certified by the Rush Interpreter Services Office. A qualified bilingual study team member who has been certified by the Rush Interpreter Services Office will be conducting outreach to Spanish-speaking parents.

POTENTIAL BENEFITS TO PARTICIPANTS
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 through the TES 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.

DATA MANAGEMENT AND CONFIDENTIALITY
Research data will be electronically recorded and stored in the following secure locations:

- Online survey data: NU's instance of REDCap
- App use data:
    - Vira App: Ksana Health's secure servers
    - Mood Education App: Feinberg School of Medicine's AWS Environment
- Text messaging/other communications with participants: Feinberg School of Medicine Servers
- Interview data: Feinberg School of Medicine Servers

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. Hard copy files will be stored in a secure location accessible only to the study team. Audio and video data will be stored on secure servers and will only be available for coding by study staff. All intervention technologies will be developed by our software development partners, Ksana Health and Audacious Software, using up-to-date security measures. The study team has worked with Northwestern University to establish contracts with these vendors to develop and maintain the digital tools that will be used to deliver the TES and CT interventions and manage the resulting data. We've laid out a description of the data handling practices for each of these vendors in table 2 below:

Table 6. Software Vendor Data Handling

Vendor	Data Collection Platform	Data Elements Handled by Vendor	Data Storage Location During Project	Data Retention at End of Project
Ksana Health	Vira Mental Health Measurement Platform	Email address to generate user login, app use event data (e.g., number of logins, time spent reviewing written information in the app), survey responses, smartphone sensor data (deidentified location data, physical activity, motion), and in-app communication with study coach	Ksana's Secure Servers	Ksana will delete all study data at the end of trial after data is transferred to the study team.
Audacious Software	Mood Education Smartphone Application	Phone number to generate user login, and app use event data (e.g., number of logins, time spent reviewing written information in the app)	NU's AWS Environment/ FSMIT on-premises servers	Data will not leave the NU environment. Data will be retained indefinitely at NU.
	Simple SMS Platform	Phone number used to facilitate sending/receiving text messages between study coach and participant, log of messages exchanged between study coach and participant	NU/FSMIT on-premises servers	

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.

Optional usability and user feedback interviews and focus group interviews:
Audio data will be stored on secure servers and will only be available for coding by study staff. Interview audio files may be transcribed by one or more of the following NU transcription vendors:
GMR Transcription https://www.gmrtranscription.com/
Wordsworth https://wordsworthcoop.com

Files may be shared via secure access to FSM servers or through vendors' proprietary web-based applications for secure file management.

Data Analysis

Effectiveness (Sub-Aim 2.1).

All effectiveness analyses for the primary (PHQ-9) and secondary clinical (GAD-7, suicidal ideation) outcomes will use intention to treat methods. A comparison of population characteristics (race and ethnicity, age, gender, health status, baseline depression and use of other mental health treatments) must be made between patients receiving TES and the control treatment. Should the populations be different, propensity scores will be estimated for the likelihood of receiving TES, and models will adjust for those scores (trimming the data as necessary). After the population comparison and appropriate adjustment, we will compare overall effectiveness, using generalized linear mixed models (GLMM) to determine if there are differences in effectiveness between individuals receiving TES and CT over time.[106] Separate models will be run for PHQ-9 and GAD-7, using participants who meet entry criteria for each (PHQ-9≥10 or GAD-7≥8, respectively). Missing data will be managed through multiple imputation. Additional covariates will also be included to identify any substantive changes in the service, technologies, and/or implementation plan as a result of optimization during the trial.

Moderation of TES on effectiveness. Moderation of patient characteristics (race, ethnicity, income, age, sex, health status, substance/alcohol use, or use of other mental health treatments, including pharmacologic) will be analyzed in individual GLM models by estimating a treatment by moderator interaction in predicting end of treatment depression scores adjusting for baseline levels of depression.

Power. This is a pilot study aimed at evaluating feasibility, and as such, sample size was not determined by power. Nevertheless, we provide an estimate of an effect size that we may be able to detect with a conservative estimate of roughly 2 enrolled participants per clinic month, or 50 participants in CT and 80 participants in TES. As power calculations for delayed roll-out trials would involve speculation of both between period and within period autocorrelations, which would be speculative at this point, we estimated an effect size for a cluster randomized trial, with estimated ICC of 0.01 within clinic. Based on this sample size, we will have 80% power to detect an effect size of 0.62 in an intent-to-treat analysis. This equates to a difference in PHQ-9 scores between CT and TES after treatment of 3.1 assuming a SD of 5.

Implementation (Sub-Aim 2.2).

We will examine the implementation outcomes: reach and cost. Reach is defined as the implementation cascade including 1) the number of eligible patients (PHQ-9≥10 at clinic visit during recruitment period); 2) number of patients consented and randomized; and 3) number of patients completed (6 or more weeks in treatment). As is common in implementation research, we will likely be underpowered for standard statistics;[102,107] we will therefore examine implementation metrics (adoption , and reach) using control charts and run charts over time, as well as charts centered on the time when clinics are transitioned from CT to TES.[108,109] These charts plot observed rates or means together with ±1 & 2 SDs and then plot the measures monthly to determine if there is significant trend or change in implementation metrics over time. To evaluate time to stable implementation in the TES arm, we will use run charts examining runs, shifts, and trends to look for nonrandom variation that indicates actual change or stability of the implementation metrics over time.[110] Cost for a depression free day (DFD), with DFD estimated using linear interpolation of PHQ-9 scores using a criterion of PHQ-9<10 and compared across conditions using both a t-test (on cost) and incremental cost effectiveness ratio (ICER) analysis.[111-113] This metric allows comparison with other studies.[114,115]

D6.3 Aim 3. Experimental Therapeutics. We will evaluate if the core UCD targets (usability, usefulness, and satisfaction) in the TES will result in increased objective and subjective markers

of engagement relative to the CT, with by testing the mediational effects of subjective and objective engagement with the apps on the primary outcomes, depression (PHQ-9) and anxiety GAD-7). Subjective engagement will be measured using the Twente Engagement with eHealth Technologies Scale (TWEETS), while objective engagement will be measure by app use (number of app launches and time from first to last use). We hypothesize that the difference between the TES and CT will be mediated by subjective and objective engagement. We also hypothesize the moderating effects of patient characteristics on subjective and objective engagement, depression, and anxiety will be lower in the TES arm, relative to CT, as a result of inclusion of users' voices through the design processes used in the creation of the TES app.

Mediation will be tested using methods by Iacobucci.[121] Using analogous adaptations of methods to Preacher's methods,[122,123] we will be able to test for moderation and mediation together. Between patient characteristics and actionable targets (subjective and objective use) we could test many moderated mediation (conditional indirect effects) which may indicate that a particular subset of participants (defined by subjective or objective use, and patient characteristics) may be more likely to benefit from TES. Multiple models will need to be fit, increasing the possibility of an inflated type I error. To prevent this, we will implement a false discover rate (FDR) control using methods by Benjamini-Hochberg[124] although as these are pilot studies, we will test these models at a FDR of 10%. Depending on the distribution of the variables under consideration, we will fit linear or logistic regression models to estimate regression parameters a (TES and the relationship to potential mediators) and b (mediator relationship to the outcome). Iacobucci shows that a normally distributed test statistic can be constructed from standardized regression parameters Za=a/SEa such that Z(mediation)=Za*Zb/(sqrt(Za2+Zb2 + 1)) can be used to test for mediation. Further, we can examine if there is further moderation of these models such that any patient covariate could moderate the relationship between TES use and depression outcomes. Power analyses for the individual RPs can be found in the RPs.

Power. While sample size and power calculations for mediational analyses are subject to speculation, Fritz and Mackinnon[116] show that our effective sample size of 112 (130 divided by the design effect determined by the number of patients per clinic and ICC within clinic) achieves 80% power to detect between a medium effect size, and small-medium effect size for the a and b paths (medium ES = 0.39, small-medium ES=0.26) using the joint tests we propose.

SMS Data and Focus Group Analysis Plan

Data from SMS records and focus groups will be analyzed qualitatively via thematic analysis as described by Braun and Clarke or via semi-open iterative coding. Semi-open iterative coding would allow us to begin with a set of codes relevant for the trial and stay open to new codes (as in thematic analysis).

Organizational Level Data

Rush University Medical Center personnel will provide aggregated data on TES Reach/Adoption on a routine basis. The Rush team will ensure a de-identified DUA is in place and will work with the Research Core to have the data extracted and de-identified prior to the transfer. Additionally, the request will be reviewed and approved by the Rush Data Governance Committee. These de identified data exports may include the following information which will enable the study team to understand what proportion of patients who screened positive for depression and/or anxiety were offered participation in the trial and engaged in TES. For patients in each participating clinic:

- Number of patients screening positive on PHQ-9, GAD
- Number of patients being referred to study

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS

CLINICAL TRIAL
Oversight of the trial is provided by the Principal Investigators, Drs. Mohr, Meyerhoff, and Stiles-Shields. The NU research coordinator, Ms. Barnas 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 that do not unblind investigators 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. Drs. Mohr, Meyerhoff, and Stiles-Shields will review adverse events (AEs) and serious adverse events (SAEs) individually in real-time and in aggregate at each DSMB meeting (not less the annually). 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.

Data Safety Monitoring Board (DSMB)
The DSMB will be chaired by Greg Simon, MD, from Kaiser Permanente, Seattle. Dr. Simon is a well-respected mental health researcher. He is well versed to chair a study that will include participants with potentially multiple minoritized identities (i.e., adolescents ages 13-17,

racial/ethnic minoritized identity, low socioeconomic status). 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. The PIs and Dr. Kwasny (biostatistician) will be present to facilitate the flow of information, however they will not be voting members.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS
CLINICAL TRIAL
All data are stored on secure servers. Collaborators working on this project have agreed to protect the data via agreements executed with Northwestern University. To protect privacy and confidentiality, all identifiable information collected via smartphone apps or messaging is encrypted at rest. Identifiers, such as the contact phone numbers from the participants contact lists are hashed, and therefore not identifiable in the research database. To help protect participant privacy, this study was awarded a Certificate of Confidentiality from the National Institutes of Health. This certificate would help us legally to refuse to disclose information that may identify participants in federal, state, or local civil, criminal, administrative, legislative, or other proceedings, if there is a court subpoena. Confidentiality may be broken by research staff to ensure the patient's safety if there is an imminent threat to self. 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. All data presentation will be of aggregate-level data; participants are never individually named and identifiable data are never presented. Researchers do not have plans to evaluate the legality of participants' behaviors, nor do we expect to gather information that would directly reveal engagement in illegal behavior. In the unexpected event that researchers do become aware of participants engaging in illegal behavior, we would protect participant confidentiality per the terms set forth in the NIH certificate of confidentiality.

<u>Limits to Confidentiality</u>
Participants will be notified during the informed consent process that a break in confidentiality may be necessary if we learn of child abuse, neglect, and/or harm to self or others. Adolescent participants (age 13-17) will be notified that their parents/guardians may have to be notified to keep them safe. As mandated by Illinois state law, all disclosures of abuse or neglect will be reported to the Department of Children and Family Services (DCFS) and all clinical staff will complete the Illinois Mandated Reporter Training (https://mr.dcfstraining.org/UserAuth/Login!loginPage.action;jsessionid=A12E50700101F9604FD9FFDBCFA136ED). A pediatric psychologist (Dr. Stiles-Shields) will be involved in managing reports of abuse and neglect.

ECONOMIC BURDEN TO PARTICIPANTS
There will be no cost to participants to receive the TES. It is possible that some participants might have very limited data plans, or text messaging plans, and the use of the study apps and coaching via text message may cause them to exceed their data limit resulting in fees. The study apps do not use unusually large amounts of data, and text messages are generally limited to a few a week, so this is an unlikely occurrence, and the study team asks about participant data plans and will inform participants of the expected data usage prior to downloading the apps. There are no procedures that will be billed to insurance.

CONSENT PROCESS
The following description of consent procedures for the clinical trial is broken into two sections. Section 1 describes general consent procedures that will apply to all subjects regardless of

age. Section 2 describes specialized procedures that apply only to the combined adolescent assent/parental consent process for participants aged 13-17.

Section 1: General Consent Procedures
The informed consent process will be electronic and will be executed through Northwestern University's instance of REDCap. Individuals engaged in the informed consent process will read through the consent form, answer a series of questions to assess comprehension, and then will be asked "do you wish to participate?".

People who answer "no" to "do you wish to participate" when completing the consent process will be prompted to let the study team know why they do not wish to participate. The response choices will include:

- I'd like to speak with a study representative before signing the consent form
- I have concerns about the study (please specify below)
- Time commitment
- Other (please specify below)

A member of the study team will follow up with all individuals who wish to speak to a study representative. Participants who answer "no" to "do you wish to participate" will not be able to execute the consent form or complete additional study procedures.

People who answer "yes" to "do you wish to participate" will be asked to type their name, electronically sign, date, and press submit.

Once the electronic consent form has been fully executed and submitted, two things will happen:

1. Participants will receive one of the following messages:
    - For subjects ages 18+: "Thank you for consenting to participate in the iCan 4 Wellness study. As a next step, you may continue on to complete the initial paid survey now, or you may press save and return to complete it at a later date. You will receive daily reminders to complete this survey within the next week."
    - For subjects ages 13-17: "Thank you for consenting to participate in the iCan 4 Wellness study. A member of the study team will review the information you provided and contact your parent or guardian to obtain their permission for you to join the study. Once we have your parent or guardian's permission for you to join the study, we will contact you with instructions for completing the initial paid survey."

2. The research coordinator will receive an electronic notification which will prompt them to confirm (1) that the form was signed by the participant and (2) that the comprehension questions were answered correctly. The research coordinator will then contact the appropriate party by telephone to follow-up on any of the comprehension questions that were left blank or answered incorrectly.

REDCap reports will be generated daily to alert the study coordinator to follow-up with subjects who have not submitted the digital consent form within 48 hours of receiving it. The coordinator will follow-up with individuals who have not submitted consent up to 3 times before discontinuing efforts to enroll the subject in the study. Participants may contact study staff at any time for a copy of the consent form for their records.

Once the informed consent process has been fully executed, the participant will proceed with study assessments and randomization to Treatment as Usual or the TES Intervention.

Section 2: Specialized Procedures for obtaining participant assent (ages 13-17)/parental consent
The adolescent assent/parent or guardian consent form is one document (administered electronically). A consent protocol that includes bilingual staff and a Spanish-language version of the assent/parent or guardian consent is in place for English-speaking minors with Spanish-speaking parents (see below).

First, participants will be presented with the IRB approved assent language. Once the adolescent participant has finished reading the assent verbiage, they will be asked to sign the assent form if they are interested in participating. Once submitted, a member of the research team will contact the parent/guardian whose child has completed the online screening and assent (parent/guardian contact information is gathered during the online screening process, as well as parent's preferred language (English or Spanish)) to inform them that their child is interested in joining the research study and ask if they are willing to review the online consent form and provide permission for their child to participate. If the parent is willing to review and sign the online consent, they will review a copy of the assent form that their child signed and they will be asked to add their own signature to the consent portion of the form (or to a Spanish-language version, as applicable). The parent/guardian will be asked to verify that they have legal authority to consent to the child's participation in the research. A research coordinator will verify that the parent/guardian has executed the consent form before engaging the adolescent participant in post-consent procedures.

Spanish-speaking Parents
Although we are recruiting only English speakers to participate in the study activities, we will be obtaining parental/guardian consent from Spanish-speaking parents as needed using a Spanish version of the informed assent/consent form. The Spanish ICF and assent have been translated and certified by the Rush Interpreter Services Office. A Rush-qualified bilingual staff (QBS) member on the study team will be obtaining permission from Spanish-speaking parents. QBS certification is granted by the Rush Interpreter Services Office after confirming the staff member's Spanish-language abilities.

Note regarding the add-on focus group: The focus group addendum will not be translated into Spanish as the study sample contains no adolescents with Spanish-speaking parents.

NON-ENGLISH-SPEAKING PARTICIPANTS
Non-English-speaking participants will not be enrolled.

PROTECTED HEALTH INFORMATION (PHI AND HIPAA)
We will collect the following PHI:

- Zip Code

Zip code is currently collected via the demographics survey on REDCap; however, due to the later addition of this self-reported variable, these data will be missing for approximately 114 participants. The missing data will be collected by IRB-approved Rush study staff via manual review of Rush's instance of Epic and securely transferred to Northwestern with a DUA in place. In most cases, the zip code data can be obtained from the "patient lookup" screen, which is a snapshot of the patient's demographics that does not require opening the medical chart.

We are requesting a HIPPA Waiver of Authorization for this activity because all 114 of these participants have completed the study (i.e., none are in follow-up). While it is feasible to reach out to the participants post-study completion to obtain permission/zip codes (we have their email addresses and phone numbers), we anticipate that the majority will not respond, resulting in a dataset that could not adequately characterize the study sample in terms of geographic location. This will make it impossible to ascertain the percentage of participants enrolled who reside in the underserved communities the study intended to reach (some of which have the highest levels of poverty, lowest life expectancy, and worst health outcomes in Chicago). Furthermore, the team will be unable to evaluate whether the intervention under investigation can reduce health disparities which are prominent across Chicagoland's communities. The activity is minimal risk in nature, as the zip code can be obtained from the demographics snapshot, which does not entail opening the record.

We are requesting a waiver of consent as this activity poses minimal risk to subjects (data are obtainable from a snapshot of the medical record that does not entail staff to open the chart, they will be entered directly into a secure platform (REDCap) and securely stored). Additionally, efforts to reach out to 114 participants for their consent may yield a low response rate, resulting in an incomplete dataset which will make it impossible for us to ascertain if we reached the communities we intended to reach (see above). The waiver of consent does not adversely affect the rights and welfare of subjects – these are data participants may already provide for payment purposes, data will be protected and shared only with approved research staff, and findings will be reported only in aggregate (without personal identifiers).

Zip codes will be manually entered directly into NU's instance of REDCap, which is accessible only to approved research staff. When downloaded from REDCap, data will be stored in secure FSM servers. The data will be stored indefinitely for future related analysis, as approved by the IRB. To protect the data from improper use or disclosure, participants' direct personal identifiers will not be released without prior consent, except as specifically required by law or for other research where the use or disclosure of the PHI is not required by 45 CFR 164.512. Efforts will be made to limit the use and disclosure of the data to people who have a need to review this information. The data manager will share stored data with collaborators who have executed data Data Use Agreements with Northwestern University.

QUALIFICATIONS TO CONDUCT RESEARCH AND RESOURCES AVAILABLE

The research staff at CBITs have extensive experience developing and evaluating remote-delivered mental health interventions.

Dr. Mohr is the Director of Northwestern University's Center for Behavioral Intervention Technologies (CBITs) and a tenured professor in the Department of Preventive Medicine. CBITs, which was founded in 2011, is a unique center in the United States, focused on the development, evaluation and implementation of technologies, including computer, mobile, and sensors, aimed at changing behavior in support of health, mental health, function, quality of life, and wellness. Dr. Mohr's work lies at the intersection of behavioral science, technology, and clinical intervention research, and is focused on developing and evaluating interventions that harness Internet and wireless technologies to promote health. This work in development includes the design, development and implementation of mobile and computer-based treatments for depression and anxiety in healthcare settings as well as the development of a context sensing mobile application that harnesses embedded mobile phone sensor data to identify behavioral phenotypes related to depression and mental health. Much of the work has involved clinical trials methods. The P50 ALACRITY center (which funds this research project) will provide a significant advancement in design and clinical trials methodology, adapting them to fit digital mental health interventions as well as implementation and sustainment. This project also is in many ways the culmination of

more than a quarter of a century of research, continuously funded by the NIMH, as we move from efficacy and effectiveness trials to solution-focused trials with the end goal of leaving a sustainably implemented digital mental health intervention in a real-world care setting.

Rush and CBITs staff have been working closely on the development of this project for several years and are collaborating to put the resources in place to conduct this study. The services being provided in this study are a supplement to standard care, and providers will continue to provide all standard care services to patients who enroll in this study.

The UIC site PI (Dr. Stiles-Shields) is a licensed clinical psychologist who has worked in clinical and research capacities with children under the age of 18 for more than a decade. She was an Assistant Professor in the Department of Psychiatry and Behavioral Sciences at Rush University Medical Center for over three years and maintains an adjunct faculty appointment there. She is now an Assistant Professor at the Institute for Juvenile Research at the University of Illinois Chicago, whose campus abuts the research site at Rush University Medical Center. The Rush site PI (Dr. Sanchez-Johnsen) is a clinical psychologist and Associate Professor and Vice-Chair for Research in the Department of Family Medicine at Rush University, with extensive experience in research with underserved and minoritized populations.

COLLABORATIVE RESEARCH PARTNERS

The collaborative research team is comprised of personnel from Northwestern University, Rush University Medical Center, The University of Illinois at Chicago, Ksana Health, and Audacious Software. The proposed roles of personnel from each site are delineated in the table below.

Table 7. Research Sites and Vendors

Site	Role	Approvals
Northwestern University (NU)	NU will serve as the lead site for this study. NU personnel will be responsible for maintaining current versions of the protocol, consent documents, and other IRB materials. NU staff will be responsible for screening and consenting study participants, collecting outcome data, delivering and supervising the TES, disbursing subject payments, managing suicidality assessments, and analyzing study data. NU staff will facilitate regular project meetings with participating sites and will be responsible for communicating procedural changes, emergent issues, interim results, and study status updates. NU will be responsible for ensuring that all sites involved in data handling have executed the appropriate agreements.	IRB protocol number STU00211887
Rush University Medical Center	Rush will serve as the main recruitment and implementation site for this study. Rush personnel will be responsible for referring study participants, monitoring delivery of the TES, managing suicidality, and facilitating access to organizational-level data . Investigators from Rush will be involved in data analysis.	A reliance agreement, executed via Smart IRB, has been uploaded to the eirb+ system.

The University of Illinois at Chicago (UIC)	Effective 9/1/22, Co-PI, Dr. Colleen Stiles-Shields, will provide study oversight from a faculty position at UIC. Dr. Stiles-Shields will be engaged in non-exempt study activities (which may include direct contact with participants and access to identifying study data).	A reliance agreement will be executed via Smart IRB. A single IRB consultation intake form was submitted on 10.7.22
Ksana Health	Software Development/Maintenance: Ksana Health established several agreements with Northwestern University to make their Vira platform available for use in delivery of the TES. Data Storage/Retention: Ksana Health will store data on their secure servers during the trial and transfer it to NU at the end of the trial. Upon termination of this Agreement Ksana Health shall erase, destroy, and render unrecoverable all Northwestern data.	The following agreements executed between NU and Ksana Health have been uploaded to the eirb+ portal. Northwestern University - FSM and Ksana Subscription Services Agreement Signed by NU 06302021.pdf Northwestern University - FSM Information Security Addendum for Ksana Health Signed by NU 06302021.pdf Northwestern University Service Level and Support Agreement for Ksana Health Signed by NU 06302021.pdf Ksana Health has passed all security vetting by FSMIT.
Audacious Software	Software Development/Maintenance: Chris Karr, Founder and CEO of Audacious Software, is working as a Northwestern University contractor and will be responsible for the development and maintenance of two pieces of software that will be deployed in the clinical trial: 1. The Mood Education app that will be used by participants randomized to CT 2. The secure text messaging dashboard that will be used to deliver the TES coaching service. Data Storage/Retention: Mr. Karr is working with FSM IT to store all data on FSMIT managed servers/cloud storage environments. Data resulting from the applications built and managed by Audacious Software will not leave NU servers.	The following agreement has been executed between Audacious Software and Northwestern University and have been uploaded to the eirb+ portal. Audacious Software - Services Agreement 2016FEB01 executed.pdf Audacious Software is not subject to FSMIT security vetting since all data will be stored in NU/FSMIT on-premises servers.

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