Project STAND (Self-guided Treatment for Adolescents Navigating Depression): a randomized controlled trial

Protocol Number: LMX-001
1/24/23

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1. Purpose of the Study and Background

1.1 Purpose of the Study

The primary aim of the proposed research is to evaluate the effectiveness of a self-guided, cognitive behavioral therapy (CBT)-based mobile app (SparkRx) + assessment-enhanced Usual Care (eUC) compared to eUC alone as an intervention for adolescents with symptoms of depression who are under the supervision of a licensed healthcare provider.

This aim will be accomplished by evaluating:

- A statistically significant difference in Patient Health Questionnaire (PHQ-8) scores ($p < 0.05$) between SparkRx + eUC (hereafter referred to as "SparkRx") and eUC alone at post-intervention as a primary outcome. The Patient Health Questionnaire (PHQ-8) is provided in Appendix 1.
- Secondary/other outcomes of intervention response, remission, intervention safety based on participant adverse events and adverse device effects, anxiety symptoms, and global functioning, as well as retention rates, program adherence, and usability ratings. 1 month follow-up data will also be evaluated.

1.2 Background

1.2.1 Adolescent depression is a major public health concern

Depression, the most common mental health disorder among adolescents and young adults, is a critical health problem within the US, ranking 4thin global burden of disease[1,2] Annual incidence of a major depressive episode among adolescents is ~3.2 million, affecting 13.3% of teenagers and increasing to 26% when including mild depressive symptoms[3]. Rates of adolescent depression are rising sharply, with global prevalence of depressive symptoms estimated to have doubled over the past few years[4]. There has also been a 56% increase in adolescent suicides in the last decade, making suicide the #2 cause of death amongst teens[5-7]. These alarming trends highlight an urgency to develop effective and accessible treatments for affected adolescents[4]. Adolescent depression has far-reaching consequences including impairments in academic and work performance and social and family relationships, substance abuse, and exacerbation of other health conditions[8-15]. Affected youth are also at a higher risk for developing a range of other mental health disorders, as well as for unemployment and physical health problems in adulthood[16-19]. Adolescent depression places significant economic burdens on the US healthcare system[20], with higher medical costs than those for almost any other mental health condition[21]. Lastly, depression is a pervasive disorder[22,23], with lifetime recurrence rates of ~70%[24,25], and a $210B societal burden annually as a whole, thus targeting this problem in adolescence, the typical time of initial onset, is critical for improving future outcomes. The proposed study is significant as it will target a critical public health concern, the urgency of which is now magnified by a global pandemic and mandated social distancing[26-28], that impacts a significant proportion of the population and is presently a leading cause of global disability in youth[29].

1.2.2 Effective care for adolescents with symptoms of depression is limited

Adolescents with symptoms of depression constitute a large group with significant unmet clinical needs. Despite high prevalence rates of depression among adolescents, very few seek treatment and they are more prone to discontinue or reject psychotherapy, due to concerns over privacy and/or stigma[30,31]. In addition, access to effective mental health care is often limited[32-34]. Demand for mental health professionals has outstripped supply, particularly in rural areas, a problem that is predicted to intensify over the next 10 years[35-38]. Waitlists for mental health providers are often at least 2-6 months long and represent one of the most substantial barriers to receiving care[39-44]. Consequently, 60-80% of adolescents with depression do not receive appropriate or timely treatment[45,46]. Mandated social distancing practices implemented during the COVID-19 pandemic magnified the already significant challenges[47,48]. Digital intervention is a solution that is needed immediately. Primary care visits provide a unique opportunity to identify adolescents with depression and direct them towards appropriate treatment. Primary care physicians often serve as a gateway for mental health treatments as official American Academy of Pediatrics guidelines recommend annual depression screening of

adolescents in primary care[49]. However, many primary care providers lack adequate time and training to provide effective psychotherapy-based treatment and approved options for pharmaceutical treatments within adolescent populations are limited, have limited effectiveness[50-52] and may pose safety concerns in youth, including side effects in 10-25% of users[53,54]. 50% of adolescents decline antidepressant use and only about a third of youth adhere to prescribed antidepressant therapy after it has been initiated in a pediatric setting[55,56]. These significant barriers highlight a critical need and opportunity for new and effective treatment options for adolescent depression that can be prescribed by primary care providers. An evidence-based, self-guided psychotherapy delivered via a prescription product and overseen by a pediatrician can be a promising adjunct to standard of care with few anticipated side effects and can overcome existing limitations in access to mental health care, adherence, and safety.

1.2.3 Digital Interventions for Symptoms of Depression in Adolescents

Accumulating evidence highlights the efficacy of digital health interventions for mental illness, providing cost-effective, convenient, and accessible means of treatment[57-59]. Digital treatments via mobile applications hold particular promise for adolescent mental illness, as youth increasingly report high levels of smartphone use[60] and enjoy using novel technologies[57]. Digital interventions can be completed at home, allowing patients to practice implementation of clinical recommendations[61] and increasing accessibility of on-demand resources. Critically, such interventions can serve as a first line of defense for treatment, reducing[57] high economic costs associated with traditional in-person psychotherapies and wait times to access clinically-validated treatment. Digital health interventions can also be less stigmatizing, leading to higher rates of engagement and self-disclosure[62-65]. Mobile applications allow for delivery of interactive content, information collection, self-report, and remote patient monitoring, which can be harnessed to personalize and enhance treatment and to intervene appropriately. The recent COVID-19 global pandemic has further underscored the urgency for safe, accessible, and effective digital alternatives to standard mental health treatments[66-69]. This need is critical for the adolescent population who are especially vulnerable to depression and suicidality following environmental stressors, trauma, and social isolation[28,48,70-74].

Cognitive-behavioral therapy (CBT) is effective in the prevention and treatment of depression in children and adolescents[75-80] and a recommended form of treatment by the American Academy of Pediatrics[81]. Digital forms of CBT[75-80], have been shown to be effective in the treatment of anxiety and depression in youth[82]. Behavioral Activation (BA)[83-87], a core CBT skill, seeks to 1) increase engagement with adaptive and contextually relevant activities that induce feelings of mastery or pleasure, 2) advance an individual's personal goals using a combination of motivational strategies, reward-seeking, natural reinforcers, and self-monitoring, and 3) reduce harmful and avoidant behaviors that often manifest during depressive episodes[83, 84, 86, 87]. Adolescents may be especially vulnerable to reward-related deficits due to immaturities in reward processing neural systems[88,89], impacting their ability to both experience reward and overcome avoidance. BA can also be helpful in treating symptoms that especially impact adolescents with depression, including withdrawal from social activities, inactivity, and avoidance[90]. BA-specific therapy offers a promising approach for treating depression in adolescents[91-93]. Given that BA is necessarily individually paced, self-driven, and self-monitored, it can be easily delivered digitally, which may be appealing to depressed youth who have limited access to or interest in traditional care. Recent evidence suggests that behavioral aspects of CBT are equally effective as cognitive approaches in reducing depressive symptoms in youth and may mechanistically drive symptomatic reduction in CBT[77,80, 89,94]. A digital BA program for adolescents with symptoms of depression represents an exciting new direction for treatment[82,95, 96]. We hypothesize that the quantity and quality of behavioral activations completed by adolescents may mechanistically explain symptom improvement in response to a digital behavioral activation focused digital intervention.

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Despite reported benefits and preliminary efficacy of digital health interventions in clinical research, the rigor of previous research is problematic as studies have suffered from small sample sizes and widespread adoption of and adherence to such interventions in clinical practice is limited[97-99]. Treatments developed in research settings are incongruous with those developed for commercial use, with the former lacking engaging content

and accessibility and the latter lacking an adequate evidence base. To our knowledge, there are no commercially available interventions nor prescription digital therapeutics specific to adolescents with symptoms of depression. We hypothesize that leveraging engaging mobile technologies will enhance treatment engagement and adherence, mediating clinical effectiveness, and ultimately reducing costs and wait times for mental health treatment for patients, closing a significant treatment gap in the care of adolescents with symptoms of depression.

2. Criteria for Subject Selection

2.1 Number of Subjects

220

Sample size calculation is based on primary outcome PHQ-8 at post-intervention. Six PHQ-8 measurements will be collected from each subject (baseline and weekly during the 5-week intervention period). Using a two-sample t-test approach, assuming a two-tailed alpha set at 0.05, a total of 200 participants (100 in each study arm) will give us 80% power to detect a moderate effect size of at least d=0.4. Given an anticipated 10% rate of attrition, we aim to enroll 220 total participants in the study.

2.2 Sex of Subjects

A 50% female sample will be targeted. Earlier recruitment efforts within the study demographic have resulted in majority female samples, consistent with prevalence rates within the study population. As such, recruitment efforts will be undertaken to ensure representation of male participants.

2.3 Age of Subjects

13-21 years old. Adolescent depression is on the rise, which can have deleterious effects on healthy transitioning to adulthood, with prevalence rates highest within this age range. The age group selected is expected to have the capacity to complete a self-guided intervention program. Recruitment efforts will be taken to ensure equivalent representation of participants under and over the age of majority (18 years old).

2.4 Racial and Ethnic Origin

Recruitment efforts will be taken to ensure adequate representation of underrepresented racial and ethnic minority groups.

2.5 Inclusion Criteria

1. 13-21 years of age
2. PHQ-8 score ≥ 5 at eligibility screening
3. English fluency and literacy (participant and legal guardian, if applicable)
4. Access to a compatible smartphone (or other device) and operating system (i.e., capable of installing the app from the Google Play or Apple App Store; list will be provided on study website [app2]) and regular internet access
5. Participant willing and able to provide informed consent/assent and have legal guardian willing and able to provide informed consent (if required)
6. Under the care of a United States (U.S.)-based licensed healthcare provider and willing and able to provide contact information for the provider and sign a HIPAA release that allows Limbix to contact provider
7. Willing and able to provide information required for study enrollment (e.g. all responses to initial PHQ-8 assessment, and current antidepressant medication status)
8. Located in the continental U.S., Hawaii, or Alaska, and not planning to leave the U.S. during the study period (through 1-month follow up assessments, up to 11 weeks after eligibility screening)

2.6 Exclusion Criteria

1. Diagnosis of (or treatment for) bipolar disorder, post traumatic stress disorder, psychotic disorder, substance use disorder, or eating disorder within the 12 months prior to eligibility screening
2. Change in psychotropic medication (initiation or change in dose) within the 30 days prior to eligibility screening
3. Plans to initiate or change treatment (e.g., psychotherapy, psychotropic medication, and/or other psychosocial treatment) for a mental health disorder during the study intervention period (5 weeks) as determined at eligibility screening
4. Suicide attempt within the past year
5. Active suicide ideation with intent
6. Previous participation in user testing or clinical testing of Spark or SparkRx, or other previous use of SparkRx app
7. Participation in any other clinical research involving a mental health intervention or treatment within 60 days prior to eligibility screening
8. Plans to participate in any other clinical research involving a mental health intervention or treatment during the study intervention period (5 weeks) as determined at eligibility screening
9. Any condition, comorbidity, or event that, in the opinion of the investigator, will prevent the participant from adhering to the protocol or benefitting from the intervention (e.g., coercion, low level of cognitive functioning) or will prevent investigators from being able to ensure safety (e.g., will be leaving the country during study time period)
10. Having a sibling who is a past or current participant in the study

2.7 Vulnerable Subjects

Children between the ages of 13-17 will be included in this research as the program to be evaluated is specifically designed as an intervention for adolescents with symptoms of depression. Assent will be obtained from all children under 18 for study enrollment unless legally emancipated or financially independent in accordance with CA state regulations and regulations of the state in which the minor resides.

3. Methods and Procedures

3.1 Procedure

Recruitment

Participants will be recruited through community sampling and provider- or healthcare system-facilitated community recruitment. Contract research organizations (CROs) and other referral-based recruitment companies may be used to contact potential participants, providers, and healthcare systems. Recruitment methods may include provider referral, media and social media ads and posts; online advertisement; flyers and other physical ads; word of mouth; and outreach to providers, community members, and potential participant pools (including but not limited to caregiver groups, youth groups, health-focused groups and organizations, schools, and healthcare systems).

Providers may be compensated at a rate of $200/hour for time spent assessing preliminary patient eligibility and referring preliminarily eligible patients to Limbix for prescreening. Specifically, providers who are compensated will be asked to complete a review of study eligibility criteria and indicate whether their patient is potentially eligible for the study (Appendix 8). Assessments of preliminary eligibility can be completed via chart review or via discussion with the patient. Potentially eligible individuals will be directed to the study landing page.

Potential participants (and legal guardians, if applicable) will be directed to a web-based landing page where they will either self-assess preliminary eligibility using an abbreviated prescreening form or be asked to indicate whether they meet sets of eligibility criteria via a full prescreening form (Appendix 3). If potential participants completing the prescreening form indicate that they are ineligible, they will be directed to a list of

mental health resources (Appendix 4). Potential participants who are unsure about their eligibility can reach out to a research team member to discuss further or will be contacted by a research team member to determine potential eligibility.

Preliminarily eligible participants (and legal guardians) will then be prompted to schedule a videoconferencing session with a research coordinator in order to complete the consenting process. Potential participants who indicate that they are under the age of 18 will be prompted to provide contact information for a parent or caregiver, who will be contacted with information about the study and/or the scheduled videoconferencing session. They will be provided with a link to access a video presentation describing all study components, participant rights, and contents of the consent/assent form, and will be asked to view the video and answer comprehension questions embedded within it before the videoconferencing session. Potential participants (and legal guardians) who have not viewed the video prior to the videoconferencing session will view it during the session. If participants do not attend their scheduled videoconferencing appointment, they may be sent an email or SMS message allowing them to reschedule their appointment.

Consent, eligibility confirmation, and enrollment

At the videoconferencing session, potential participants (or legal guardians, if required) will confirm their identity by presenting an approved form of U.S. identification. They will be asked to reschedule their appointment if they are unable to do so. If participants under the age of 18 do not have their legal guardian present, they will also be asked to reschedule. Potential participants (and legal guardians) will then receive a brief overview of study components, during which they will respond to comprehension checks, and have the opportunity to clarify any questions or concerns. If participants (and legal guardians) did not watch the video presentation describing all study components provided before the videoconferencing session, they will watch the video during the videoconferencing session in place of this brief overview. Participants will be informed that they will be randomly assigned to either the SparkRx or the eUC only condition and will be provided with comprehensive information about the consent form and their rights as research participants (for details, see section 8.2). After providing their full names and email addresses, a Part 11 compliant electronic signature will be obtained from the participant (or legal guardian) to document consent. Documented e-assent will be obtained for participants under 18 years of age. Emancipated minors and/or minors who are financially independent will be allowed to provide informed consent in accordance with federal guidelines, CA state regulations, and regulations of the state in which the minor resides. Participants who turn 18 during their participation in the study will be asked to provide informed consent once they reach the age of majority.

Following consent, participants and legal guardians will be asked to provide their preferred email address, preferred phone number for receiving text messages, information about their mobile device, home address, current address (in case safety concerns arise), and emergency contact information. Participants will be required to provide the name and contact info for their healthcare provider. To confirm that providers are licensed in the U.S., research coordinators will search for the provider in the National Provider Identifier (NPI) records directory (https://npiregistry.cms.hhs.gov/search). If a participant is unable to provide their healthcare provider's contact info, or the research coordinator is unable to confirm the provider's NPI record, the participant will be asked to provide the information of another healthcare provider. If the participant is unable to do so, they will be instructed to reschedule the appointment to a time when they can provide another provider's information, or they will be deemed ineligible. Participants (or legal guardians) will be asked to sign a HIPAA release form to allow Limbix to contact their healthcare providers.

To confirm that participants are located in the United States, they will be asked to provide the Internet Protocol (IP) address of the device they are using during the videoconferencing session. Research staff will determine whether the IP address is located within the U.S. by entering it into a known lookup website. IP address lookup is generally accurate (>90%) for determining whether a device is located within or outside the U.S. However, because IP addresses are not perfect indicators of location, if participants insist that they are within the U.S. despite providing a non-U.S.-based IP address, the enrollment will continue with the provision

that further checks of IP address will be conducted using location information already collected through the secure web portal and app. Participants whose location cannot be confirmed to be within the U.S. will be dropped from the study, as safety cannot be appropriately monitored and ensured for these individuals.

A participant account in a secure web portal will be created with a username (user email addresses) and a temporary password. Potential participants will log in to the portal and will be instructed to change their password. In the portal, potential participants will complete two forms needed to determine eligibility: the PHQ-8 and the Medication Use Screener (see Appendix 1). Potential participants who do not meet criteria for participation based on the PHQ-8 (score < 5) or who do not wish to (or cannot) respond to the Medication Use Screener will be informed of their ineligibility and directed to mental health resources.

Participants and legal guardians (if applicable) will then be asked to verbally confirm that they meet each eligibility criterion. To ensure privacy, legal guardians will be asked to leave the room unless the participant indicates that they want their guardian present. After confirming eligibility with the participant, the legal guardian will be asked to return and confirm the eligibility of their child. Participants who report a history of suicidal ideation or self-harm urges will be prompted to complete a safety plan in collaboration with the resarch coordinator and/or study clinician (Appendix 5). If participants endorse active suicidal ideation with intent during this session, they will be directed to seek an emergency psychiatric evaluation for further assessment of their risk and appropriate intervention (see section 4.8.1). Participants (or legal guardians) who indicate ineligibility to participate due to any of the other eligibility criteria will be directed to alternative mental health resources and will be ineligible to continue with participation. Participants who are ineligible as a result of having an incompatible mobile device/operating system will be sent an email offering the opportunity to schedule another video session if their device/operating system changes. All eligible participants will be provided with a safety plan document and instructions for completing and using this safety plan document should it be necessary (Appendix 5). An emailed or text reminder to complete this plan may be sent following the consent session.

Participants will be asked to indicate in weekly participant symptom checks (PSCs; see Appendix 1) or to notify the study team if their treatment for symptoms of depression or any other health condition changes during the study, or if they participate in any other treatment/intervention research study. Participants will be encouraged to follow the advice of their doctor regarding all medical decisions. Participants will be told that this is a blinded study, meaning that most of the study staff with whom they interact after randomization will not know whether they received the SparkRx app or not. They will be provided with contact information if they need to reach out for app or web portal troubleshooting, or with questions about their participation in the study.

After eligibility is confirmed, an account for legal guardians (if applicable) in the secure web portal will be created with usernames (user email addresses), and legal guardians will be provided a temporary password to log in to change their password. Participants and legal guardians (if applicable) will be directed to complete baseline assessments in the secure web portal. Upon completion of baseline assessments, participants will be randomized (1:1) to either the SparkRx condition or the eUC only condition (see descriptions below). Randomization will be stratified by participant-reported antidepressant medication status ([yes, no] from the Medication Use Screener) and participant-reported baseline PHQ depression severity (low: PHQ-8 score <15; high: PHQ-8 score ≥15). Participants will receive instructions on how to download and log into their assigned mobile app. Following randomization and app download, the session will end. Additional information will be sent to participants via email.

Following the videoconferencing session, research coordinators will contact participants' healthcare provider offices and indicate that the patient has enrolled in this research study. If information is volunteered to the research coordinator that the participant is not a patient of the healthcare provider, the participant will be contacted to provide information for an alternative healthcare provider. As participant safety may be compromised in the absence of a known U.S.-based healthcare provider, participants will be dropped from the

study if contact information for an alternative healthcare provider is not obtained.

Intervention Period

SparkRx group: The SparkRx mobile program will be 5 weeks in duration and self-guided. The five modules in this program are each expected to take around 60 minutes to complete. Modules do not need to be completed in a single session but can be completed over the course of several days. Emergency resources for participants experiencing thoughts of suicide or self-harm will be available in the app. While participants can progress through the programs at their own pace, participants will be instructed to complete one module in the mobile app per week, and to complete the program within the 5-week intervention period. Participants will be prompted to complete weekly PHQ-8 and PSC in the mobile application. App notifications, text (SMS) and/or email messages may be sent to participants to encourage them to complete the weekly assessments (i.e., PHQ-8 and PSC). To encourage participants to engage with the app, automated app notifications will also be sent. For participants under 18 years of age, legal guardians may receive email and/or text notifications to complete proxy PHQ-8 and PSC assessments in the secure web portal.

eUC group: Participants will download a mobile app that contains no content, but that provides access to in-app weekly PHQ-8 and PSC assessments.

All participants will receive notifications (app notifications and SMS and/or email) to complete the PHQ-8 and PSC). For participants under 18 years of age, legal guardians may receive email and/or text notifications to complete proxy PHQ-8 and PSC assessments in the secure web portal .

Post-intervention period

After the 5-week intervention period, all participants will be sent links via email and/or text to complete post-intervention self-report questionnaires in the secure web portal. Participants may receive automated email and text reminders to complete the post-intervention questionnaires. A study coordinator may also contact participants (and legal guardians) who have not completed post-intervention questionnaires before they reach a 2 week deadline.

One month after the end of the intervention period, participants will be prompted to complete self-report questionnaires to evaluate sustained effects of the intervention on relevant outcomes. Participants may receive automated email and text reminders to complete the questionnaires. A study coordinator may contact participants (and legal guardians) who have not completed follow-up questionnaires before they reach a 2 week deadline. Participants who do not complete the one-month follow-up questionnaires within 2 weeks will be considered lost to follow-up.

If a participant chooses to withdraw from the study at any point or the participant is dropped from the study during the intervention period (5 weeks), access to the web portal and mobile app will be restricted at that time; otherwise access to the mobile app will be restricted at the end of week 5 and access to the web portal will be restricted after 1-month follow-up assessments have been completed or the participant is deemed lost to follow-up.

All relevant FDA requirements for the conduct of clinical trials will be followed, including registration on clinicaltrials.gov. Email and other notification templates are provided in Appendix 6.

3.2 Description of the Limbix SparkRx Program

The SparkRx program is a 5-week program divided into 5 levels intended to be completed weekly. A character called 'Limbot' is used as a guide. Limbot encourages the user in completing the behavioral activation program and provides personal examples of how they have undertaken behavioral activation therapy. Participants are instructed to complete a weekly PHQ-8 assessment and PSC in the mobile app. Tasks in the mobile app

progress in a linear fashion -- i.e., each task must be completed to progress to the next task. Certain on-demand resources can be accessed in the app at any time, including crisis resources. Text entries that match a database of concerning words/phrases will trigger an automated pop-up suggesting participants visit the in-app crisis resources if they need additional support. Study staff will monitor participants' freeform text, symptom deterioration, pop-up alerts, and questionnaire data for safety.

3.3 Description of assessment-enhanced Usual Care (eUC)

UC is based on a stepped care model for treatment for symptoms of depression. It can include any of the following: active monitoring of depressive symptoms and suicidality, supportive counseling by a healthcare provider, psychosocial support interventions, collaborative care (e.g. facilitation of parental and patient self-management, referral for peer support or other community or school-based behavioral health programs), psychoeducation, complementary and alternative medicine approaches, psychotherapy (e.g. behavioral treatment, interpersonal therapy, cognitive behavioral therapy), pharmacotherapy for mood problems, visit to a primary care provider, behavioral or mental health specialist or therapist, counselor or coach for mood disorder. For purposes of this study, UC will be enhanced by prompting participants to complete weekly PHQ-8 and PSC assessments in a mobile app. Study staff will monitor participants' symptom deterioration and questionnaire data for safety.

3.4 Assessments

The following Prescreening, Baseline, post-intervention, and follow-up assessments will be completed via secure web portal. Weekly participant assessments (PHQ-8, PSC) will be completed in the mobile app. Weekly legal guardian assessments (PHQ-8, PSC proxies) will be completed via the secure web portal. All assessments are provided in Appendix 1, with the exception of the Prescreening Questionnaire (Appendix 3).

Table 1. Schedule of Assessments

	Eligibility Screening	**Baseline**	**Weekly during intervention period**	**Post-intervention**	**1-month follow-up (4 weeks post intervention)**
Prescreening Questionnaire	X (if used)				
Patient Health Questionnaire (PHQ-8)	X		X	X	X
Medication Use Screener	X				
Baseline Questionnaire		X			
Baseline Questionnaire, legal guardian proxy*		X			
Patient Health Questionnaire (PHQ-8, legal guardian proxy*)		X	X	X	X
Behavioral Activation for Depression Scale - short form (BADS)		X		X	X
Generalized Anxiety Disorder (GAD-7)		X		X	X
Pediatric Quality of Life Enjoyment & Satisfaction Questionnaire (PQ-LES-Q)		X		X	X
Pediatric Quality of Life Enjoyment & Satisfaction Questionnaire (PQ-LES-Q, legal guardian proxy*)		X		X	X
Participant Symptom Check (PSC)			X	X	X

Participant Symptom Check (PSC, legal guardian proxy*)			X	X	X
Post-Intervention Questionnaire				X	
Post-Intervention Questionnaire, legal guardian*				X	
Systems Usability Scale (SUS)				X	
User Engagement Scale (UES-SF)				X	
1 month follow-up Questionnaire					X
1 month follow-up Questionnaire, legal guardian*					X
Absenteeism Questionnaire		X		X	X
Healthcare Utilization Questionnaire		X		X	X
Absenteeism Questionnaire, legal guardian*		X		X	X
Healthcare Utilization Questionnaire, legal guardian*		X		X	X

* Only administered when participants are under 18 years of age

Description of Assessments

- The **Prescreening Questionnaire** is administered to potential participants on the study website landing page and assesses whether or not participants are preliminarily eligible to participate based on yes/no/unsure responses to clustered sets of eligibility criteria (Appendix 3).
- The **Patient Health Questionnaire (PHQ-8) Participant and Legal Guardian Proxy** is an 8-item participant-report measure for screening for depression and for establishing depression severity[100]. The total score ranges from 0-24, with a higher score indicating greater depression symptom severity. For participants under 18, a legal guardian proxy version of the PHQ-8 will be administered to legal guardians. Clinically significant improvement is defined as a reduction in assessment score ≥ 5[101]. Intervention response is defined as 50% reduction in symptoms from pre- to post-intervention, and remission is defined as a score < 5 following intervention[102].
- **Medication Use Screener** is a single-item screening form that asks participants to report whether or not (yes/no) they are currently taking psychotropic medication for the treatment of depression or symptoms of depression.
- **7 item Generalized Anxiety Disorder scale (GAD-7)**. The GAD-7 is a validated 7-item participant-reported assessment for generalized anxiety disorder[103]. We will evaluate changes in anxiety symptoms given the high comorbidity between anxiety and depression. The total score ranges from 0-21, with a higher score indicating greater anxiety symptom severity.
- **Pediatric Quality of Life Enjoyment & Satisfaction Questionnaire (PQ-LES-Q) Participant & Legal Guardian:** A 15-item participant-reported self-administered questionnaire that captures life satisfaction over the past week[104]. Each question is rated on a 5-point scale from 1 (Very Poor) to 5 (Very Good). The first 14 items are summed to form a total score ranging from 14-84, with higher scores indicating higher quality of life. The 15th item (“Overall, how has your life been?”) is a stand-alone item. For participants under 18, a legal guardian proxy version of the PQ-LES-Q will also be administered to legal guardians.
- **Participant Symptom Check (Participant and Legal Guardian).** Assesses legal guardian- and participant- reported negative symptoms and changes in treatment since the last check-in, using multiple choice and free-form text responses.
- **Behavioral Activation for Depression Scale - Short Form (BADS).** The BADS[105] consists of 9 participant-reported questions assessing behavioral activation and avoidance over the previous week, each rated on a 7-point scale ranging from 0 (not at all) to 6 (completely). This form can be used to track behaviors hypothesized to underlie depression and specifically targeted for change by behavioral activation. It examines changes in the following areas: activation, avoidance/rumination, work/school impairment, and social impairment. The total score ranges from 0 to 54, with higher scores indicating higher activation.
- **Baseline Questionnaire (Participant and Legal Guardian).** This participant- and legal guardian-reported questionnaire includes participant age, sex, gender, socio-economic status, medical

history, and medications.

- **Post-Intervention Questionnaire (Participant and Legal Guardian).** This participant- and legal guardian-reported questionnaire assesses feedback on the mobile app.
- **System Usability Scale (SUS)**. The SUS[106]is a participant-reported scale that provides a quick, reliable tool for measuring the usability of the mobile app. The SUS consists of a 10-item questionnaire with five response options for respondents, ranging from Strongly Agree to Strongly Disagree. The total score ranges from 0-100, with higher scores indicating greater usability.
- **User Engagement Scale - Short Form (UES-SF).** The UES-SF[107]is a participant-reported, statistically reliable measure of self-reported user engagement that is tailored to the specific device being tested (i.e., the study app). The form has 12 items and uses a 5-point Likert scale. There are 4 subscales: Aesthetic appeal, focused attention, perceived usability, and reward. Each subscale score ranges from 1-5, with higher scores indicating higher levels of each scale. The total score also ranges from 1-5, with higher scores indicating more engagement.
- **One month follow-up Questionnaire (Participant and Legal Guardian).** This participant- and legal guardian-reported questionnaire assesses feedback on the mobile app.
- **Absenteeism Questionnaire (Participant and Legal Guardian)** This participant- and legal guardian-reported questionnaire assesses missed time at work and/or school attributable to the participant's mental health condition over the past 4 weeks.
- **Healthcare Utilization Questionnaire (Participant and Legal Guardian)** This brief participant- and legal guardian-reported questionnaire assesses use of healthcare resources over the past 4 weeks.

4. Data Analysis and Data Monitoring

4.1 Primary Outcome

- The primary outcome measure is depressive symptom severity (PHQ-8 score), which will be used to compute differences in mean depressive symptoms between participants randomized to the SparkRx condition and those randomized to the eUC condition at post-intervention (5 weeks). PHQ-8 score will also be used to determine whether there is clinically-meaningful reduction in severity in the SparkRx group at post-intervention. Clinically-meaningful reduction in severity is defined as a 5 point or greater decrease in PHQ-8 score from baseline.

4.2 Secondary Outcomes

- Intervention response at post-intervention (50% reduction in PHQ-8 score from baseline)
- Remission at post-intervention (PHQ-8 score < 5)
- Clinically-meaningful reduction in severity at post-intervention (≥5 point reduction in PHQ-8 score from baseline)

4.3 Tertiary/Exploratory Outcomes

- Legal guardian-reported PHQ-8 score at post-intervention
- Anxiety symptoms (GAD-7) at post-intervention
- Participant- and legal guardian-reported global functioning (PQ-LES-Q) at post-intervention
- Participant- and legal guardian-reported absenteeism at post-intervention
- Participant- and legal guardian-reported healthcare utilization at post-intervention
- Behavioral activation (BADS) at post-intervention
- Participant-reported app usability and engagement (SUS, UES-SF)
- Primary, secondary, and tertiary/exploratory outcomes at 1-month follow-up (as appropriate)

4.4 Intervention Compliance Outcomes

- Intervention adherence (rates of module and program completion) for SparkRx group
- App usage (daily active users, minutes spent in app) for SparkRx group

4.5 Safety Outcomes

- Number of adverse events (AEs), number of participants with AEs, and rates of AEs based on

PHQ-8-based symptom deterioration and responses to weekly PSC questionnaires (both groups)
- Number of AEs, number of participants with AEs, and rates of AEs based on in-app freeform text (SparkRx group only)
- Number of adverse device effects (ADEs), number of participants with ADEs, and rates of ADEs (SparkRx group only)

4.6 Sample Size

Sample size calculation is based on primary outcome PHQ-8 at post-intervention. Six PHQ-8 measurements will be collected from each subject (baseline and weekly during the 5-week intervention period). Using a two-sample t-test approach, assuming a two-tailed alpha set at 0.05, a total of 200 participants (100 in each study arm) will give us 80% power to detect a moderate effect size of at least d=0.4. Given an anticipated 10% rate of attrition, we aim to enroll 220 total participants in the study.

4.7 Data Analysis

Detailed statistical analysis plans (SAP) will be developed prior to completion of primary outcome data collection. Prior to analysis, study population details including the number randomized to each study arm and lost to follow-up will be described. Baseline participant characteristics will be summarized for the SparkRx and eUC arms as means, standard deviations, medians, 25^{th} and 75^{th} percentiles for continuous variables, and as counts and percentages for categorical variables. Differences in baseline characteristics between the groups will be explored using tabular and visual displays, as appropriate, and appropriate statistical tests (e.g., independent sample t-tests for continuous variables, chi-square tests for categorical variables).

4.7.1 General Approach

Analysis Populations: All analyses will be completed in line with the intention-to-treat (ITT) principle, where all participants will be included in the analyses according to their assigned study arm at baseline, regardless of adherence to study protocol. Per-protocol analyses will also be conducted to estimate treatment effects for participants who adhered to the protocol, and will include individuals who completed the Baseline and post-intervention PHQ-8 assessments and, for participants in the SparkRx group, met a minimum engagement threshold of completing two modules.

Descriptive Statistics: For descriptive statistics, the following will be reported:

Continuous data: n, mean, standard deviation, median and interquartile range, minimum and maximum

Categorical: n/N and percentage of total per arm

Missing Data: We do not anticipate missing data for the stratification variables, which will be included as covariates in the analysis models. Ongoing efforts will be made to reduce the amount of missing data for all outcomes. Despite these efforts, missing data for primary, secondary, and tertiary/exploratory outcomes are likely. Data missing at random (MAR) on dependent variables are easily handled in repeated measures mixed models so no imputation will be needed. For all other statistical analyses described below and missing data on covariates (or independent variables) in models, multiple imputation will be used if at least 5% of data points are missing for a given covariate or variable. Case analysis or single imputation methods may also be used and a specific approach for imputation will be selected based on key attributes of the obtained data, including percent missing and whether data are missing at random. We will compare the results obtained with and without imputation. Sensitivity analyses will be used to assess the impact of potential deviations from the MAR assumption on the study findings.

4.7.2 Analysis of Primary Outcome

To test the primary hypothesis that there will be a difference between the SparkRx and eUC arms such that participants randomized to receive SparkRx will have lower PHQ-8 scores at post-intervention, we will implement a mixed effect model with appropriate correlation matrix. Time (i.e., day after Baseline session [T=0] that each PHQ-8 was completed), intervention arm, time by intervention interaction, baseline PHQ-8 score, and antidepressant medication status (variable used for randomization) will be included in the model as fixed effects. We will test different correlation matrices such as UN, CS, AR(1), and select the best correlation

structure for our data. The hypothesis will be tested as two-sided with a significance level of 0.05. This primary analysis will be conducted according to the ITT principle with participants analyzed and outcomes attributed according to the treatment arm to which the participants were randomized, regardless of post-randomization compliance. We will additionally determine whether the stated threshold for clinically-meaningful reduction in severity based on PHQ-8 (reduction in score ≥5 from baseline) is included or surpassed by 95% confidence intervals around the average PHQ-8 reduction in the SparkRx arm.

4.7.3 Analysis of Secondary Outcomes

We will compute the number and proportion of participants meeting criteria for intervention response, remission, and clinically-meaningful reduction in severity at post-intervention for each group, and compare rates between groups using chi-square tests. We hypothesize that there will be higher rates of intervention response, remission, and clinically-meaningful reduction in severity in the SparkRx arm than in the eUC arm.

4.7.4 Analysis of Tertiary/Exploratory Outcomes

For each continuous outcome (e.g., GAD-7, BAD, PQ-LES-Q), scores at post-intervention will be compared between groups using analysis of covariance (ANCOVA) models, with baseline scores included as a covariate.

To test the hypothesis that legal guardian-reported depression symptoms (PHQ-8 proxy) will be lower for the SparkRx group than the eUC group at post-intervention, we will implement a mixed effect model with appropriate correlation matrix as described above (4.7.2).

Moderation analyses will be carried out to determine if and how participant characteristics (baseline PHQ score, antidepressant medication use, sex/gender, and age) influence intervention effects on PHQ-8 scores at post-intervention. Mediation analysis will be carried out to determine whether intervention engagement (e.g., module completion rate, duration of use, time to complete program) mediates the effect of intervention on PHQ-8 scores at post-intervention.

Changes in healthcare utilization and absenteeism from baseline to post-intervention will be examined descriptively. Ratings of app usability and engagement (SUS, UEF-SF) will be examined descriptively for the SparkRx group only.

Outcomes collected at the 1-month follow-up time point will be analyzed as above.

4.7.5 Analysis of Intervention Compliance Outcomes

We will evaluate intervention compliance descriptively by computing daily mobile app usage and time spent in the app for the SparkRx group. Likewise, rate of module completion (reaching the end of an entire module) and program completion (reaching the end of the final module) for the SparkRx group will be examined descriptively.

4.8 Data Monitoring

This is a low risk research study.

The data and safety monitoring plan for the proposed study will include monitoring of adverse events and adverse device effects by a Medical Expert, an independent external clinician, as well as by an independent Data and Safety Monitoring Board (DSMB). The following procedures will be followed, in compliance with IRB requirements, to ensure the safety of study participants and the validity and integrity of data. Because the investigational device is a non-significant risk device, the Medical Expert will not be on call 24/7.

The study investigators, Medical Expert, and study clinicians will regularly monitor potential risks and procedures for protecting risk. Study investigators and appropriate study personnel will evaluate the progress

of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, and other factors that may affect study outcome. They will also consider factors external to the study, such as scientific or therapeutic developments that may have an impact

on the safety of the participants or the ethics of the study.

Ongoing quality control will also include regular data verification and protocol compliance checks to be performed by the PIs and appropriate study personnel. An ongoing review of study procedures will be carried out to ensure that the privacy of participants and confidentiality of data as outlined in the study protocol and consent form are not violated. There will also be provisions for monitoring the collected data to ensure the safety of participants and to maintain the confidentiality of the research data.

This study may be stopped prior to its completion if: 1) study recruitment or retention is too low for the study to provide meaningful results; 2) new information becomes available during the trial that necessitates stopping the trial; 3) other situations occur that might warrant stopping the trial. The trial will be stopped early if PIs, in collaboration with the Medical Expert and the independent DSMB, find that the harm to study participants outweighs the benefit of the scientific evidence to be accrued by continuing the trial.

PIs along with the Medical Expert and study clinicians will provide continuous, close monitoring of all reported adverse events (AEs) and adverse device effects (ADEs). In compliance with IRB and DSMB guidelines, investigators will report adverse events and adverse device effects as required.

An adverse event is defined as any unwanted medical occurrence that occurs during the study. An adverse device effect (ADE) is an adverse event related to the use of an investigational medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the installation, the operation, or any malfunction of the investigational medical device. This also includes any event that is a result of a user error or intentional misuse.

For this study, ADEs may occur in only the SparkRx arm.

An adverse event or adverse device effect is considered serious if it meets any of the following criteria:

- Is fatal;
- Is life-threatening, meaning, the participant was, in the view of the investigator, at immediate risk of death from the reaction as it occurred;
- Leads to persistent or significant disability/incapacity, i.e., the event causes a substantial disruption of a person’s ability to conduct normal life functions;
- Requires or prolongs inpatient hospitalization;
- Is an important medical event, based on appropriate medical judgment, that may jeopardize the participant, or the participant may require medical or surgical intervention to prevent one of the other outcomes above.
    - Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the investigational protocol, without serious deterioration in health, is not considered a serious adverse event.
    - Note 2: Serious adverse device effect (SADE): adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

The degree of certainty of causal relationship of an ADE to the mobile investigational device will be rated as follows:

- Not Possible: An event that is not due to the use of the study device. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s) is clear.
- Possible: An event that might be due to the use of the study device. An alternative explanation - e.g., concomitant drug(s), concomitant disease(s) - is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
- Probable: An event that might be due to the use of the study device. An alternative explanation is less likely - e.g., concomitant drug(s), concomitant disease(s). The relationship in time is suggestive.
- Definitely: An event that is due to the use of the study device. The event cannot be reasonably

explained by an alternative explanation - e.g., concomitant drug(s), concomitant disease(s).

Unanticipated Adverse Device Effects (UADEs, as defined in 21 CFR 812.3, also referred to as “Unanticipated Problems”): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application; OR any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

UADEs must meet all the following criteria:

- Serious (as defined above)
- Associated with the device under investigation (possibly, probably, or definitely)
- Unexpected

No serious ADEs are expected. Given that psychotherapy and psychoeducation can lead individuals to think more about their depressive symptoms, expected ADEs may include temporary clinically significant deterioration in depressive symptoms and worsening mood. Anticipated AEs, given the study population, include suicidal ideation, non-suicidal self injury ideation, non-suicidal self injury (NSSI) that does not result in medical attention, clinically significant deterioration in depressive symptoms. Anticipated serious AEs that would be seen in this population independent of the study, include active nonsuicidal self injury resulting in medical attention, suicide attempts, death by suicide, and/or inpatient hospitalization unrelated to planned hospitalization for a pre-existing condition. Serious AEs will be reported biannually to the DSMB and to the IRB per local policy and as part of annual reporting unless they meet the definition of an UADE or unanticipated problem.

The seriousness of an AE or ADE will be preliminarily determined by study clinicians, but final determination will be provided by an independent external clinician to eliminate bias in classification. All AEs must have their relationship to the investigational devices assessed by an external clinician based on the temporal relationship and his/her clinical judgment. The study clinicians and Medical Expert will be responsible for determining whether an ADE is expected or unexpected. An ADE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

All AEs, ADEs, and complaints will be recorded. The external clinician and the Medical Expert will determine whether it is in the participant’s best interest to remain in the study after any serious AE or UADE and notify the PI accordingly.

Study PIs will report UADEs to the IRB and DSMB within 10 working days. Limbix will immediately conduct an evaluation of any reported UADEs and will report such effects to the FDA within 10 working days. If it is determined that an UADE presents an unreasonable risk to subjects, the investigation or parts of the investigation presenting that risk will be terminated as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first receives notice of the effect. Limbix will not resume a terminated investigation without IRB approval and, if the investigation was terminated under paragraph (b)(2) of 21 CFR 812.46, FDA approval.

Per 21 CFR 56.108(b)(1) and 21 CFR 812.150(a)(1), PIs will report any unanticipated problem involving risk to human subjects or others to the IRB no later than 10 business days from the time of identification. An unanticipated problem must meet all the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given the information provided in research-related documents and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research; AND
- Suggests that the research places subjects or others at a greater risk of harm than was previously

known or recognized.

4.8.1 Study Staff Responsibilities

If suicide ideation is endorsed at any point during the study, a safety protocol will be initiated. If participants are found to have a high suicide risk, they will be excluded from the research study and participants will be directed to appropriate local resources. A participant has high risk for suicide if they endorse ideation with a plan or intent. All safety incidents will be documented and reported to the DSMB, IRB, and FDA as needed.

If safety risks related to suicidality are identified during a study session, a brief suicide screening assessment (e.g., Self-Injurious Behavior Thoughts and Behavior Interview (SIBTI) may be conducted (Appendix 7). If there is an immediate concern for safety, the participant will be directed to go to the nearest ER or call 911/local behavioral health emergency responders. The study clinician will be alerted and triage safety risk as per the study safety protocol. The study clinician will contact the participant and emergency contact as needed, provide resources, and determine whether additional steps are necessary.

Symptom deterioration will be defined as a PHQ-8 score ≥ 15 and a ≥ 5-point increase from baseline or a PHQ-8 score ≥ 20 at two consecutive timepoints. If a deterioration event occurs, an alert will be sent to the study team. Freeform text entered in the mobile app, PSC assessments, and deterioration alerts will be reviewed by study staff daily. Any correspondence from a study participant will also be reviewed. If a safety concern is identified (including endorsements of or thoughts of self-harm, harming others, or others are harming them), a study team member will notify a study clinician. The contacted study clinician will review all deterioration events and concerning freeform text and reach out to participants and emergency contacts if indicated, as per the study safety protocol. The Medical Expert clinician will determine the outcome of adverse events and unanticipated adverse device effects in consultation with the independent external clinician. Data about individual safety concerns, AEs, ADEs, and outcomes of clinical reachout may be securely shared with participants' healthcare provider or referring healthcare system upon written authorization by the participant and/or legal guardian as part of the informed consent process.

Keywords or phrases that may indicate suicidality, self-harm, or harm to others will trigger an automated pop up within the mobile app directing the participant to contact emergency resources if their safety is at risk. Emergency contact information will be kept on file for all participants and participants' physical location and phone number will be obtained/confirmed to allow for effective follow up if the need arises.

Medical Expert: A qualified and experienced licensed clinician will serve as the Medical Expert. The Medical Expert will review all mental-health related serious AE and all ADEs at the time they are reported. The Medical Expert may request a meeting of the DSMB to review safety data. At a minimum, the Medical Expert will review the outcomes of serious AEs or ADEs and the causal relationship of the AEs to the investigational device. If no serious AEs or ADEs prompt review at an earlier time point, the DSMB will review AEs and ADEs at the regularly scheduled biannual meetings. The Medical Expert will also consult with an independent external clinician to verify safety classifications. Following an initial classification of the safety event as an AE or ADE by the Medical Expert, the independent external clinician will review the safety event and make a separate determination of the classification. When discrepancies between the two parties occur, the classification made by the independent external clinician will be maintained.

The study clinicians are licensed healthcare providers and have experience in the assessment of mood and anxiety symptoms, directing the treatment of such symptoms, and addressing possible adverse reactions during clinical trials. The Medical Expert will assess the benefits and risks of the protocol on an ongoing basis and will be available to the study team for questions regarding inclusion/exclusion criteria, protocol conduct, and safety. The Medical Expert will review and evaluate information relevant to the safety of this study before the implementation of the protocol and will recommend alterations to the study design based on review of subject safety trends.

Study personnel will review all data collection materials on an ongoing basis for data completeness and accuracy as well as protocol adherence. Protocol deviations and violations will be reported in accordance with IRB and FDA guidelines. In this study, a protocol violation includes but is not limited to randomization of an ineligible participant and failure to obtain informed consent/assent. A protocol deviation includes but is not limited to minor deviations from protocol that do not impact safety or efficacy and failure to keep IRB approval up to date.

A formal Data and Safety Monitoring Board (DSMB) will be assembled in accordance with NIH and NIMH criteria to ensure that the safety of study subjects is protected and that the scientific goals of the study are being met. The team assembled for the DSMB will have relevant and complementary expertise in adolescent psychiatry, clinical trial design, digital health, and statistics. Specifically, the members of the DSMB will include a child psychiatrist with expertise in depression and related disorders, a biostatistician with expertise in clinical trial design and analysis, and an expert in digital health. Importantly, none of these individuals will be involved in any other capacity with this study or have any potential conflicts of interest in study-related outcomes.Additionally, an independent unblinded, non-voting statistician will review the validity of data summarized in reports provided to the DSMB and serve as a consultant during meetings.

The DSMB will meet (e.g. teleconference) prior to the start of intervention to review and provide recommendations regarding the research protocol, informed consent/assent documents, and plans for data safety and monitoring. Subject recruitment will be initiated after review of the study protocol by the DSMB. The DSMB will then meet on a biannual basis or twice during the study duration to assess data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, any breaches of confidentiality, as well as the ethics of this trial. Detailed information will be provided to the DSMB prior to each of the scheduled meetings. This report will include a range of information on study procedures, measures, family responses, methodology, and acceptability of the intervention and measures, as well as AEs, ADEs, and SAEs experienced by study participants. Data on study progress and protocol integrity will be provided to the DSMB to ensure that the study is moving forward as planned. The DSMB Chairperson may convene additional meetings when deemed necessary.

Within 2 weeks of meeting, the DSMB will provide a written report of their recommendation to the study PIs including any modifications and recommendations. The DSMB will also make recommendations at any time to the sponsor (Limbix), the NIMH (as deemed necessary), and the study PIs concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the trial. Any recommended changes or adjustments about the study will be considered. If it is determined that the recommendations cannot be followed, the sponsor and study PIs will provide an explanation of why they cannot be followed to the DSMB and the NIMH. The IRB will receive a blinded summary report of safety findings on an annual basis from the study PIs. This data and safety review as well as an assessment of protocol compliance and data quality will facilitate the early detection of safety signals and will maximize the likelihood of continued appropriateness of the research and protection of human subjects. The review will also ensure that participants who experience AEs are provided with proper and, if necessary, ongoing attention. Any recommendations to improve participant safety, protocol adherence, or data quality will also be included.

The study PIs will also ensure subject privacy and research data confidentiality. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Unblinded data will not be released to the study investigators unless necessary for safety reasons.

Study PIs will report UADEs to the DSMB chair within 10 business days of being notified. Reported information for each UADE will include detailed information about the event timeline, the subject's medical history and current conditions, and other relevant data. Further details about DSMB processes and responsibilities are found in the DSMB Charter.

5. Data Storage and Confidentiality

Ethical guidelines for clinical research will be followed. All information obtained will be kept strictly confidential except as required by law and as otherwise indicated in this protocol and informed consent forms. We will comply with all mandated reporting rules. All researchers must demonstrate through training and testing up-to-date understanding of and commitment to follow all the guidelines and rules related to HIPAA, human subjects research, and good clinical practice that apply to this research.

Special care will be taken to prevent unauthorized access to data files. Limbix-owned computers on which data files will be accessed will have password-protection. All study participants will be assigned participant ID numbers upon enrollment in the study and all subsequent data processing will be completed by reference to these numbers. The file linking participant ID number to personal identifying information will be stored in a secure, HIPAA compliant database. Case report forms will be stored on Google Drive with a business agreement in place protecting those files. Only research staff who require access for study-related activities have permissions to view and/or edit these files. Efforts will be taken to ensure that information obtained from healthcare systems or providers that contains personal identifying information (such as the names of referred study participants) will be received through secure channels (e.g., secure email) and stored in or transferred to a secure, HIPAA compliant database.

Signed electronic consent forms will be stored through Part 11 compliant services.

The data generated by the mobile client or web portal (used for baseline and post-intervention assessments for participants and legal guardians) will be stored in an Aptible PostgreSQL database, which is backed up daily to geographically separate regions and encrypted at rest. After the study, the data will continue to be stored in said database. In the event that we need to decommission the database, we will move the data to cold storage in either Google Cloud Platform or Amazon Web Services (AWS) for the remaining length of time required to comply with GCP and will configure those buckets to be encrypted at rest as well. An anonymized copy of a portion of the study data will be synced daily to Google Cloud Platform for easier analysis. This copy of the data will have sensitive fields such as email, phone number, and first name removed and still require a valid Limbix employee login for access.

Access to the database requires SSH login to Aptible ephemeral containers that generate logs every time an employee logs in. Accounts on Aptible are limited on a need basis and employees are assigned to roles based on the level of access they need to the system. The roles with access to the database are Account Owners and Enclave Owners only.

There will be a researcher portal where Limbix staff can view aggregate and individual participant data of accounts that are enrolled in the study. Accounts on the researcher portal have access to study data limited by roles. The roles with access to study data are System Admin, Study Admin (PIs), Study Operator, and Read-only. All content on the researcher portal will require valid login credentials with password protection.

Data generated by the mobile client or web portal will also be visible through an admin portal. Accounts on the admin portal will be limited to employees that need access in order to run and maintain technical infrastructure. All access to the admin portal will require valid login credentials with password as well as a one-time MFA password.

Anonymous usage data (such as button clicks and screen navigation) generated by the SparkRx mobile client will be aggregated using Google Analytics. All access to this data will require a valid Limbix employee login for access.

The mobile application will also require valid login credentials with password protection to access individual account information. If the mobile app does not communicate with the server for 30 days, the user will be signed out of their account automatically and have to re-login to access their data in the mobile application. After participants have completed study participation, they will be marked as completed by a research staff member via the researcher portal and access to the mobile application will be restricted.

Only designated study staff will directly contact study participants via phone or email per the study protocol to answer study-related questions. Text and email communication is encrypted in transit but unencrypted when being sent or received. Other staff may interact with participants to troubleshoot software issues that may arise. Study clinicians may contact participants and/or legal guardians if safety concerns arise, including worsening mood, in order to mitigate risks.

Communications will recommend that participants complete research-related activities including the virtual consent process in a private location. The research coordinator will conduct all research-related activities in a private room where individuals beyond the research investigators and staff cannot overhear the conversation. Participants are expected to complete the self-guided SparkRx program at a location of their choice.

No data with subject identifiers will be released, unless authorized by study participants and legal guardians, and all data obtained will be stored and maintained in a secure manner. All publications or reports of data will be anonymous in relation to subject identification. Protected health information will be disclosed to health care providers or referring healthcare systems only upon written authorization of the participant and/or legal guardian as part of the informed consent process. Data Use Agreements will be in place before protected health information is shared with referring healthcare systems. Data will be stored in a confidential manner after the research is completed in accordance with GCP. The PIs will retain responsibility for ensuring that data are maintained in a secure manner.

De-identified data or a limited data set may be shared for future research by Limbix after a Data Use Agreement is signed, where appropriate.

6. Transition from Research Participation
N/A

7. Risk/Benefit Assessment
7.1 Risk Category
Minimal risk

7.2 Potential Risk
Psychological risks: Some personal questions about life experiences or mood may bring up uncomfortable feelings.

Loss of confidentiality: As this study involves the use of identifiable, personal information, there is a chance that a loss of confidentiality will occur though steps to mitigate this risk have been taken as described below.

7.3 Protection Against Risk
To minimize psychological risks, participants will be instructed that they can choose not to answer any question in any assessment, and can discontinue their participation at any time. Because baseline PHQ-8 score and current antidepressant medication use are required for study randomization, participants will be informed that if they choose not to respond to these questions, they will not be able to continue their participation in the study. In addition, because the SparkRx mobile app progresses in a linear fashion, questions in the mobile program must be answered to progress to the next task. During consent, participants will be informed that they may discontinue their participation at any time. Patient responses to assessments completed weekly will be monitored as well as free response answers to questions delivered via the mobile app. This will enable detection of deterioration in clinical status. If such deterioration occurs, research staff will immediately contact the PI/study clinician/Medical Expert. Participation will be terminated if clinical evidence indicates that continuing would not be in the best interest of the subject as determined by the Medical Expert in consultation with a study clinician. Participation will also be terminated if the Medical Expert determines that the subject's

safety cannot be adequately monitored and/or circumstances would prevent the safety protocol from being implemented (e.g., participant's location cannot be confirmed to be within the U.S., healthcare provider indicates that participant is not their patient and alternative provider information cannot be obtained in a timely fashion). Weekly symptom reporting will also help the research team to identify any psychological or physical health consequences of study participation and, in consultation with study clinicians and the Medical Expert, determine the best way to mitigate further risks to participant health.

No medications will be withheld; however, participants will be asked to report changes to mental health-related treatment while participating in the research study.

To minimize risks to privacy and/or confidentiality, only personnel with training in protecting private information about human subjects will have access to study data. Special care will be taken to prevent unauthorized access to data files.

Computers on which data files will be accessed will have password-protected access. All study participants will be assigned code numbers on entry to the study and all subsequent data processing will be completed by reference to these numbers. Special care will be taken to prevent unauthorized access to the database or case report forms connecting participant identity to subject numbers.

All publications or reports of data will be anonymous in relation to subject identification. Protected health information will be disclosed to other professionals treating the participant only upon written authorization of the participant (or legal guardian). PIs will retain responsibility for ensuring that files are maintained in a secure manner during and after study.

Study staff will ensure that no individuals outside the authorized team can overhear conversations during the virtual sessions. Participants in the study will be expected to complete mobile interventions at a location of their own discretion with respect to privacy and confidentiality.

Although every reasonable effort has been taken, confidentiality during Internet and phone-based communication procedures cannot be guaranteed and it is possible that additional information beyond that collected for research purposes may be captured and used by others not associated with this study.

Any data shared in the future will be stripped of all identifying information and protected health information or a limited data set may be shared with a Data Use Agreement, when applicable.

7.4 Potential Benefits to the Subjects

No direct benefits can be guaranteed by participating in this research protocol. As participants in the intervention arm will receive a mobile program designed to be therapeutic, they may experience direct benefits from participation in terms of reduced symptoms of depression, as well as potential reductions in comorbid anxiety symptoms, and improvements in mood, and/or functional outcomes.

Participants may also directly benefit from participating in the proposed research because of the knowledge obtained. Assessments and procedures completed during the study may provide participants with an opportunity to reflect on their thoughts, feelings, and behaviors which may be valuable in helping individuals better understand their own emotional functioning. These benefits outweigh the minimal risks associated with this trial. Participants will have the opportunity to provide feedback about the intervention to help improve the program for future users. This ability to help others may also have therapeutic benefits for participants.

7.5 Alternatives to Participation

Prospective participants who decline to enroll in this study are free to consider alternatives, including seeking

treatment. Standard of care treatment for adolescent depression typically includes psychotherapy with or without antidepressants, depending on clinically determined variables. Mental health resources will be shared with potential participants who decline to participate in this study but are treatment-seeking. However, alternative treatments are not promised or guaranteed. Participants may also participate in another research study or not seek any treatment.

8. Subject Identification, Recruitment and Consent/Assent

8.1 Method of Subject Identification and Recruitment

Participants will be recruited through community sampling and provider- or healthcare system-facilitated community recruitment. Contract research organizations (CROs) and other referral based recruitment companies may be used to contact potential participants, providers, and healthcare systems.

8.2 Process of Consent

Prior to participation, electronic consent will be obtained for all participants over 18. For participants under 18, electronic assent will be obtained, and electronic consent will be obtained from a legal guardian unless the minor is legally emancipated or financially independent in accordance with CA state regulations and regulations of the state in which the minor resides. Any trained member of the research team will be authorized to obtain informed consent/assent.

For consent processes that are completed virtually via videoconferencing, to ensure participant privacy, the research staff member conducting the consent process will ensure that no one outside of the research team can overhear the consent process from their end and will recommend that the potential participant join the videoconference from a private location. The researcher will provide an explanation of the study and the consent form (live or video-recorded), take time to answer any questions, provide time for decision-making, and request an electronic signature.

Participants (and legal guardians, where applicable) will be informed that their participation is voluntary, they are free to discontinue participation at any time, and all information will be kept confidential, except: 1) legally-mandated exceptions to confidentiality, e.g., if a participant reports that they are at risk of harming themselves or someone else, or that someone is harming them, and 2) legal guardians of minor participants will be informed when a study clinician determines that clinical contact with the participant or legal guardian is warranted. For example, legal guardians will be contacted if a participant under 18 years of age exhibits potential worsening of psychological symptoms as indicated in app freeform text or weekly check-in responses. Participants will be told that freeform text entries in the mobile app during the study will be reviewed, but not in real time. It will be clearly communicated to all participants that this intervention is not intended to prevent suicide attempts or self-harm behaviors and that the intervention is not for emergency care. All potential risks or discomforts will be explicitly listed and explained. Participants will also be asked to indicate whether or not they'd be willing to be contacted regarding future research opportunities. Participants will be asked if de-identified written or spoken statements they provide during the study can be used in any marketing materials or publications and can opt out from allowing any de-identified statements they provide to be shared.

Consent forms, as well as verbal presentations (videoconference and video), will additionally emphasize:

1) This is a research study testing an investigational medical device intended as a treatment for symptoms of depression;
2) Possible (minimal) risks and benefits of participation;
3) Participants can elect not to respond to any question(s) they are not comfortable answering, with the exception of the baseline assessments required for study enrollment;
4) Participants can choose to end their participation at any time for any reason;
5) All information will be kept confidential with the exception of certain information that must be reported for legal or ethical reasons including suspected child abuse or neglect, suspected elder abuse or neglect, or

intent to harm oneself or others.

The consent process will be considered complete only if the participant (and legal guardian, if applicable) demonstrates comprehension of all study procedures. This will be determined through comprehension questions and conversation with study staff. After all questions concerning the study have been fully answered by study staff, a Part 11 compliant, electronic signature will be obtained from the participant to document consent. Documentation of the assent of a minor will also be obtained. Participants (or legal guardians) will be required to display a valid form of identification to verify identity. Participants will be provided with a link to access and download a copy of the signed consent/assent form at any time. Signed electronic consent/assent forms will be stored in a HIPAA compliant server.

If a minor will become of legal consenting age during their participation in the study, they will be required to consent at that time to continuing their participation.

8.3 Subject Capacity

The study will not enroll participants who are unable to provide consent or assent (if potential participants are under 18). Discussions between potential participants and research staff members during the videoconferencing session will disclose any obvious additional comprehension problems or physical limitations that would prohibit participation. Cognitive and physical limitations that would preclude participation are included as part of study eligibility criteria.

8.4 Subject Comprehension

All participants will view a video recorded explanation, scripted at a 5th grade reading level, of the purpose, procedures, and potential risks of the study and of their rights as research participants. Participants (and legal guardians) will be given ample time and opportunity to carefully review the consent/assent form and ask questions regarding this study to study staff, family, friends, and/or doctors prior to signing. Understanding will be confirmed by specific questions presented to potential participants (and legal guardians) during the consenting process.

8.5 Debriefing Procedures

No information will be purposefully withheld from participants.

8.6 Consent Forms

The following informed consent forms are being submitted with this protocol:

1. Informed Consent

8.7 Documentation of Consent

A Part 11 compliant, electronic signature will be obtained from the participant (or legal guardian) to document consent. Documentation of the assent of a minor will also be obtained. Participants will be provided with a link to access and download a copy of the signed consent form at any time. Signed electronic consent/assent forms will be stored through Part 11 compliant services.

8.8 Costs to the Subject

Participants are expected to provide payment for clinical care that is not part of this research protocol (e.g., hospitalization costs) through standard health care payment procedures. Participants will have no costs associated with research participation, beyond those associated with phone and internet usage. Limbix will pay for all procedures associated with the study or necessary study-related follow-up.

8.9 Payment for Participation

Participants will be compensated for completing assessments, including baseline, in-app, post-intervention,

and 1-month follow-up questionnaires. The payment amount will be determined based on whether they complete (“full compliance”), partially complete (“partial compliance”), or do not complete (“no compliance”) study questionnaires at each timepoint. Compensation for participants randomized to the SparkRx intervention will not be contingent on completion of mobile app modules during the intervention period. Caregivers who attend the videoconferencing session with their child will be compensated for their time. Participants and caregivers will be paid in the form of electronic gift cards.

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