

A CBT-based mobile intervention as first line treatment for adolescent depressive symptoms during COVID-19

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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, CBT-based mobile app intervention (Limbix Spark) compared to an educational control condition for the treatment of teens with depressive symptoms under the supervision of a healthcare provider during the COVID-19 pandemic.

This aim will be accomplished by evaluating:

- Statistically significant change in pre to post treatment depressive symptoms (as measured by PHQ-8) between Limbix Spark and web-based educational control condition as a primary outcome
- Secondary outcomes of remission rates (PHQ-8 score <10), intervention safety based on participant (and parent, where applicable) clinical concerns, anxiety symptoms, and global functioning, as well as retention rates, program adherence, and usability ratings

### 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 4<sup>th</sup> in global burden of disease<sup>1,2</sup>. 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<sup>3</sup>. Rates of adolescent depression are rising sharply, with a 63% increase over the past 5 years<sup>4</sup>. There has also been a 56% increase in adolescent suicides in the last decade, making suicide the #2 cause of death amongst teens<sup>5-7</sup>. These alarming trends highlight an urgency to develop effective and accessible treatments for affected adolescents<sup>4</sup>. 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<sup>8-15</sup>. 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<sup>16-19</sup>. Adolescent depression places significant economic burdens on the US healthcare system<sup>20</sup>, with higher medical costs than those for almost any other mental health condition<sup>21</sup>. Lastly, depression is a pervasive disorder<sup>22,23</sup>, with lifetime recurrence rates of ~70%<sup>24,25</sup>, 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<sup>26-28</sup>, that impacts a significant proportion of the population and is presently a leading cause of global disability in youth<sup>29</sup>.

#### 1.2.2 Effective care for adolescents with depression is limited

Adolescents with 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<sup>30,31</sup>. In addition, access to effective mental health care is often limited<sup>32-34</sup>. Demand for mental health professionals has outstripped supply, particularly in rural areas, a problem that is predicted to intensify over the next 10 years<sup>35-38</sup>. Waitlists for mental health providers are often at least 2-6 months long and represent one of the most substantial barriers to receiving care<sup>39-44</sup>. Consequently, 60-80% of adolescents with depression do not receive appropriate or timely treatment<sup>45,46</sup>. Mandated social distancing practices implemented during the COVID19 pandemic are expected to magnify the already significant challenges<sup>47,48</sup>. 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<sup>49</sup>. 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<sup>50-52</sup> and may pose safety concerns in youth, including side effects in 10-25% of users<sup>53,54</sup>. 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<sup>55,56</sup>. 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 Cognitive Behavioral Therapy Interventions for Adolescent Depression**

Accumulating evidence highlights the efficacy of digital health interventions for mental illness, providing cost-effective, convenient, and accessible means of treatment<sup>57-59</sup>. Digital treatments via mobile applications hold particular promise for adolescent mental illness, as youth increasingly report high levels of smartphone use<sup>60</sup> and enjoy using novel technologies<sup>57</sup>. Digital interventions can be completed at home, allowing patients to practice implementation of clinical recommendations<sup>61</sup> and increasing accessibility of on-demand resources. Critically, such interventions can serve as a first line of defense for treatment, reducing<sup>57</sup> 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<sup>62-65</sup>. 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<sup>66,67</sup> has further underscored the urgency for safe, accessible, and effective digital alternatives to standard mental health treatments<sup>68,69</sup>. This need is critical for the adolescent population who are especially vulnerable to depression and suicidality following environmental stressors, trauma, and social isolation<sup>48,70-75</sup>.

Cognitive-behavioral therapy (CBT) is effective in the prevention and treatment of depression in children and adolescents<sup>76-80</sup> and a recommended form of treatment by the American Academy of Pediatrics<sup>81</sup>. Digital forms of CBT<sup>76,77,79,80,82</sup>, have been shown to be effective in the treatment of anxiety and depression in youth<sup>83</sup>. Behavioral Activation (BA)<sup>84-87</sup>, 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<sup>84,85,87,88</sup>. Adolescents may be especially vulnerable to reward-related deficits due to immaturities in reward processing neural systems<sup>89,90</sup>, 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<sup>91</sup>. BA-specific therapy offers a promising approach for treating depression in adolescents<sup>92-94</sup>. 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. In contrast, cognitive aspects of CBT require therapist input to challenge the patient's thinking, which is challenging to implement in a digital format. Moreover, cognitive aspects of CBT may be especially challenging for adolescents due to developmental immaturities, for those with learning disabilities, comorbid neurodevelopmental disorders or delays, or as a consequence of their depression<sup>91</sup>. 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<sup>80,95,96</sup>. A digital BA program for adolescent depression represents an exciting new direction for treatment<sup>83,97,98</sup>. 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.

Despite reported benefits and preliminary efficacy of digital CBT 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<sup>99</sup>. 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 adolescent 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 depression.

## **2. Criteria for Subject Selection**

### **2.1 Number of Subjects**

A convenience sample of participants will be recruited via online advertising, social media, word of mouth, flyering, and recommendations by doctors, schools, and other youth and/or health-focused organizations. Limbix may also work with participant recruitment companies, such as TrialFacts and Dynata. Healthcare providers involved in identifying potential study participants may be compensated for recruitment efforts (based on hourly effort and not on number of referrals or enrolled participants). A total of 60 participants will be recruited in Phase I, and a minimum of 120 participants with PHQ-8  $\geq 10$  will be recruited in Phase II. A statistically powered Phase III study will be designed following completion of Phase II.

Preliminary power calculations revealed that a sample size of 175 will achieve 80% power to detect a moderate effect size (Cohen's  $d=0.5$ ) between Limbix Spark and active control at a significance level of 0.05 for a two-tailed t-test with an estimated 27% attrition rate<sup>100</sup>. A moderate effect size is expected based on previous digital interventions with active controls for depression<sup>101-102</sup> and evidence of superior efficacy for CBT-based interventions<sup>102</sup>. An effect size will be calculated at the end of Phase II and may inform power calculations in determining sample size for Phase III.

### **2.2 Gender of Subjects**

Given prevalence rates of depression by gender, we expect to recruit at least 50% female participants but no gender quotas will be set for enrollment. Based on the predominant recruitment of females in Phase I, recruitment efforts in Phase II may be taken to ensure a more balanced gender representation.

### **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 treatment program.

## **2.4 Racial and Ethnic Origin**

A convenience sampling approach will be taken without firm quotas for enrollment based on racial or ethnic characteristics. Recruitment efforts may be taken in Phase II to ensure adequate representation of underrepresented racial and ethnic minority groups.

## **2.5 Inclusion Criteria**

### **Phase I**

1. Between the ages of 13 and 21
2. Self-reported symptoms of depression
3. Will be residing in the USA for the duration of the 5-week study
4. Under the care of a US-based primary care and/or licensed mental healthcare provider and willing and able to provide the name and contact information of the provider during consent appointment
5. English fluency and literacy of adolescent and consenting legal guardian if under 18
6. Access to a smartphone (iPhone 5s or later or running Android 4.4 KitKat or later) and regular internet access
7. Willing to provide informed e-consent/assent and have legal guardian willing to provide informed e-consent if under 18

### **Phase II**

1. Between the ages of 13 and 21
2. Self-reported symptoms of depression
3. Stable for at least two months on any treatment (including medication or psychotherapy) for a mental health disorder
4. Will be residing in the USA for the duration of the up to 12-week study
5. Under the care of a US-based primary care and/or licensed mental healthcare provider and willing and able to provide the name and contact information of the provider during consent appointment
6. English fluency and literacy of adolescent and consenting legal guardian if under 18
7. Access to a smartphone (iPhone 6s or later and running iOS 13.0 or later or running Android 4.4 KitKat or later) and regular internet access
8. Willing to provide informed e-consent/assent and have legal guardian willing to provide informed e-consent if under 18 (unless minor is legally emancipated or financially independent under relevant state laws)

## **2.6 Exclusion Criteria**

### **Phase I**

1. Self-reported lifetime suicide attempt or active self-harm or active suicidal ideation with intent
2. Have a diagnosis by a clinician of bipolar disorder, substance use disorder, or any psychotic disorder including schizophrenia
3. Incapable of understanding or completing study procedures and digital intervention as determined by participant, patient/legal guardian, healthcare provider, or clinical research team

### **Phase II**

1. Self-reported lifetime suicide attempt or active self-harm or active suicidal ideation with intent

2. Have a diagnosis by a clinician of bipolar disorder, substance use disorder, or any psychotic disorder including schizophrenia
3. Incapable of understanding or completing study procedures and digital intervention as determined by participant, patient/legal guardian, healthcare provider, or clinical research team
4. Previously participated in user testing or clinical testing of Limbix Spark

## **2.7 Vulnerable Subjects**

Adolescents between the ages of 13-21 will be included in this research as the program to be evaluated is specifically designed to treat 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**

Participants will be recruited via online advertising, social media, word of mouth, flyering, and recommendations by doctors, schools, and other youth- and/or health-focused organizations. Potential participants will be directed to a web-based landing page where they will read a description of the research procedures, review study eligibility criteria, and indicate whether they are eligible and interested in participation. Potential participants will use an online calendar to schedule a virtual consent appointment with a study coordinator.

The virtual consent process will involve a video conference call during which the study coordinator will describe the research procedures, give the participant and their legal guardian (if required) time to review the consent form, and answer any questions they may have in accordance with good clinical practice (GCP) and human subjects research guidelines. Potential participants will be told that their participation is voluntary, that they are free to discontinue participation at any time, and that all information will be kept confidential with the exception of 1) mandatory limits to confidentiality and 2) safety concerns for participants or others. Participants will be told that they are free to refuse to answer any question during study interviews or questionnaires and that they can discontinue participation in the research at any time for any reason. All potential risks or discomforts will be explicitly listed and explained. Participants will be asked to notify the research team if changes to their treatment for depression or another mental health condition changes during the course of the study in order to determine if it is in the best interest of the participant to continue in this research. During consent, participants and their legal guardian (if required) will be asked to indicate whether they'd be interested in participating in a post-intervention interview about their experience with the program. Participants will also be asked to indicate whether or not they'd be willing to be contacted regarding future research opportunities. After all questions concerning any aspect of the study have been fully answered by study staff, a Part 11 compliant, electronic signature will be obtained from the participant or their legal guardian (if required) to document consent. Documentation of the assent of a minor will also be obtained. Participants or their legal guardian will be required to display a valid form of identification to verify identity. If the participant will turn 18 during the time period in which the participant will be engaging in research activities, and required consent from a legal guardian at the time of enrollment, a follow up consent appointment will be scheduled with the participant for them to consent as an adult of legal consenting age to continuing their participation in the study. If such consent cannot be obtained within a reasonable time frame, participation in the study will be terminated. Emancipated minors and/or minors who are financially independent will be allowed to provide informed consent without a legal guardian in accordance with federal guidelines, CA state regulations, and regulations of the state in which the minor resides.

After consent, the study coordinator will ask participants and their legal guardian (if required) to verbally confirm study eligibility. If eligibility is not confirmed, participants will be informed that they are ineligible for participation and will be directed to a list of mental health resources available on the Limbix website. If eligibility is confirmed, the study coordinator will create subject accounts for participants and parents (if required) with usernames (participant/legal guardian email addresses) and temporary passwords. Mobile phone numbers and email addresses will be collected at this time from participants and their legal guardian, if required, and entered into a secure researcher portal. Provider name and contact information will also be collected. Date of birth will also be collected to confirm the participant's age and determine whether 17 year old participants will reach the age of majority during their participation in the study. Lastly, the participant's home address and emergency contact will be collected in case an emergency arises during the study and the participant cannot be reached via phone. If this is the case, an additional consent appointment will be scheduled for after the participant turns 18, before the completion of their participation in the study. The research coordinator will generate emails to be sent to participants and their legal guardian, if required, to reset their account passwords. Upon account creation, participants will be randomized to either the Limbix Spark condition or the educational control condition (see descriptions below).

The research coordinator will direct participants and parents to a 21 CFR Part 11 compliant web portal where they will log in with their account credentials and complete baseline self-report assessments (see Assessments below). The research coordinator will send an email to the participant and their legal guardian (if required) with a safety plan document and instructions for completing and using this safety plan document should it be necessary. A reminder email to complete the safety plan will be sent to participants and their legal guardian (if required) 3 days later. The study coordinator will remain on the video call as participants and their legal guardian (if required) complete self-report assessments. After the study coordinator confirms that the assessments have been completed, the study coordinator will text or email the participant a link to download the study mobile app from the app store and will instruct them on how to download the Limbix mobile app. Participants will sign in using their login credentials, will undergo onboarding and be prompted to complete a baseline PHQ-8 in the mobile app. Completion of this initial PHQ-8 will be required for study participation to allow safety monitoring of symptom deterioration. Based on the randomization procedure, participants will have access to either the Limbix Spark intervention or the educational active control condition. The study coordinator will provide instructions on using the program to which the participant was assigned, answer any questions and end the video call.

Both mobile programs (Limbix Spark and educational control) will be fully self-guided, completed by participants at home. Each program is designed to be completed over 5 weeks but users may progress through the program at their own pace. The Limbix Spark program progresses linearly, i.e., a task must be completed before a participant can progress to the next task. Content for a given week is not expected to take more than 60 minutes to complete. All participants will be prompted to complete a weekly PHQ-8 and clinical concerns questionnaire in the mobile app. Automated app notification reminders to complete these questionnaires will be sent. If users have not opened the app in 3 days, an automated app notification encouraging participants to use the app will be sent. An automated reminder notification will be sent 7 days before the end of the intervention period to remind participants that the intervention period will be ending in 7 days.

The legal guardian of participants under 18 will be emailed links to complete a parent-reported participant symptom check weekly. If they have not completed the questionnaire, they will be sent a reminder email 6 days later to remind them that the questionnaire is due the next day.

After the 5 week intervention period, participants and their legal guardian (if required) will be emailed links to complete post-intervention self-report assessments via secure web portal. Participants and their legal guardian (if required) will receive automated email reminders to complete the post-intervention assessments after 6 days if they have not completed the assessments. If participants or their legal guardian do not complete the post-intervention assessments within a week the research coordinator may reach out to participants or legal guardians via phone or email to encourage them to complete these assessments.

There will be two phases of this study. Phase I will evaluate feasibility of a minimum viable product (MVP) version of the Limbix Spark mobile app (Version 1) within the context of a real world deployment. After feasibility is established, Phase II will be initiated during which a primary outcome of effectiveness of the Limbix Spark app will be evaluated. At the commencement of Phase II, an updated version of Spark (Version 2) will be implemented. In order to quickly support teens during COVID-19 with an engaging and efficacious digital treatment, one additional app update is planned (Version 3) during Phase II. Recruitment for Phases I and II may not be powered to detect statistically significant differences between Spark and the educational control condition. Participants in Phase I will be randomized using a 1:1 ratio. Participants in Phase II will be randomized using a block randomization approach to ensure equal group sizes. Block size will range in multiples of 2 from 4-12 and be randomly generated to prevent guessing of allocation and eliminate bias.

In Phase I if the participant does not complete the post-intervention assessments within 4 weeks from the end of the intervention period they will be considered lost to follow up. If a participant chooses to withdraw from the study at any point or is deemed lost to follow up or 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 the 5-week intervention period and access to the web portal will be restricted after post-intervention assessments have been completed or the participant is deemed lost to follow up (4 weeks after intervention period). Participants will be compensated \$25 in the form of an electronic gift card or cash transfer for completing the post-intervention assessments regardless of adherence to their assigned intervention. Gift cards will be emailed to participants.

In Phase II, for participants randomized to the treatment arm, if the participant does not complete the post-intervention assessments within 2 weeks from the end of the intervention period they will be considered lost to follow up. If a participant chooses to withdraw from the study at any point or the participant is deemed lost to follow up or 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 the intervention period and access to the web portal will be restricted after post-intervention assessments have been completed or the participant is deemed lost to follow up (2 weeks after intervention period).

Participants randomized to the control arm will have two weeks to complete the post-intervention assessments. Once the post-intervention assessments have been completed or 2 weeks have passed, whichever occurs first, participants in the control arm will be granted access to the treatment condition (Limbix Spark) for 5 weeks. After access to Limbix Spark for 5 weeks, participants will have two weeks to complete another set of post-intervention assessments. If a participant chooses to withdraw from the study or the participant is deemed lost to follow up during the control app intervention period or Limbix Spark app intervention period (5 weeks



each), 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 each intervention period and access to the web portal will be restricted after the second set of post-intervention assessments have been completed or the participant is deemed lost to follow up (2 weeks after Limbix Spark intervention period).

In Phase II, if participants report a change in their treatment for a mental health disorder while enrolled in the study, they may be withdrawn from the study.

In Phase II, all participants will be compensated \$25 in the form of an electronic gift card for completing the baseline assessments and \$25 for completing each set of post-intervention assessments regardless of adherence to intervention (1 set of post-intervention assessments will be completed if assigned to the treatment arm and 2 sets of post-intervention assessments will be completed if assigned to the control arm-- 1 after completing the control app and another after subsequently completing the Limbix Spark app.) Gift cards will be emailed to participants.

If participants indicated during the consent process that they would be interested in participating in a post-intervention feedback interview, a research coordinator may contact participants and their legal guardian (if under 18) to set up this interview to be conducted over video conferencing. Participants who were randomized to the control condition may be contacted to complete these interviews following completion of the control arm, prior to starting the treatment condition. Participants and their legal guardian will be asked, separately, to answer questions about their experience with the program and provide feedback that may help improve the product for future users. These interviews may be audio-recorded with permission. These interviews are expected to take 1 hour, and participants and parent/legal guardians who participate will be compensated \$25/hr. Reimbursement will be prorated for interviews lasting less than 1 hour. For participants randomized to the control arm in Phase II, this interview will occur after completion of the Limbix Spark intervention period.

All relevant FDA requirements for the conduct of clinical trials will be followed, including registration on [clinicaltrials.gov](http://clinicaltrials.gov).

### **3.2 Description of the Limbix Spark Program**

The Limbix Spark program is a 5 week program divided into 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 he/she has undertaken behavioral activation therapy. Participants are instructed to complete a weekly Patient Health Questionnaire (PHQ)-8 assessment and participant symptom check 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 emergency resources for patients experiencing thoughts of suicide or self-harm.

#### **3.2.1 Release Version 1 (Phase I)**

In Limbix Spark Version 1, the level system is framed around the idea that the app is teaching a skill (behavioral activation) and as participants progress through the program, they are building this skill and becoming more of an expert at it. The different levels are:

- Level 1 (Learning): Complete the learning part of the app
- Level 2 (Growing): Complete two activations

- Level 3 (Doing): Complete 3 activations
- Level 4 (Practicing): Complete 4 activations
- Level 5 (Mastering): Complete 5 activations

## UI Architecture

- **Tabs**
  - **Home tab.** The default screen the participant lands on when opening the app.
    - Shows participant current level and progress through it.
    - Shows participant the next action they need to take and provides direct access to that action (e.g. direct link to the next learning task or to review an activity).
    - Has crisis resources
    - Gives users the opportunity to provide product feedback.
  - **Learning tab.** Contains the 6 learning activities that are done during the program
    - Spark Overview
    - Mood & behavior 1 & 2
    - Breaking the cycle
    - Identify your values
    - Intro to activity scheduling
  - **Activities tab.**
    - View upcoming activities
      - See and edit scheduled activities
      - See and access activities that need review
    - View past activities
- **Activity scheduling button**
  - A floating button that is available on any screen and allows the participant to schedule a new activity

## Program Flow

- Level 1: Learning tasks
  - Onboarding.
    - Choose a Limbot
    - Enter name
    - View a walkthrough tutorial of the app interface.
    - Learn about weekly levels
      - Level 1 (Learning): Learning part of the app
      - Level 2 (Growing): Complete two activations
      - Level 3 (Doing): Complete 3 activations
      - Level 4 (Practicing): Complete 4 activations
      - Level 5 (Mastering): Complete 5 activations
  - Overview
    - Description of the program and how it works.
  - Mood and behavior 1 & 2
    - Learn the BA model of depression, focusing on the relationship between mood and behavior, and how that leads to a downward cycle of depression. The participant identifies common feelings and associated avoidance behaviors.
  - Breaking the cycle

- Learn how to break the downward spiral of depression by changing behavior
  - Identify values
    - Complete values clarification task and learn that choosing activities that align with values helps activities to be more effective in treating depression.
  - Intro to activity scheduling.
    - Participant is taught how to schedule activities using the activity scheduling button and tab.
    - View walkthrough tutorial of the Activities tab
    - See messaging that Level 1 is completed, Limbot acknowledgement and celebration!
    - Review next level's goals, and see a reminder about trying to advance one level per week
- Level 2 through 5: Activity scheduling
  - Schedule activities and review them
    - Participant schedules activity based on values.
    - Participant reflects on activity.
  - With each level they complete, they receive Limbot acknowledgement and a celebration. They then learn about their next goal.
    - If they complete level 5 before the 5 week study is done, participant is encouraged to continue scheduling activities in the app until the study ends.

### 3.2.2 Release Version 2 (Phase II)

Release version 2 expands on version 1 with the addition of new features and content based on product feedback from participants in a recently completed feasibility study of a Spark prototype. Minor modifications may also be made based on feedback from participants who received version 1.

Features/content to be added:

- Interactive psychoeducation focusing on the TRAP (trigger/response/avoidance pattern) and TRAC (trigger/response/alternative coping) model of depression and how it relates to behavior activation.
- A mood tracking feature that enables users to practice recognizing the relationship between their mood and their behavior. The feature will accomplish this by prompting users to log activities that they have done and how those activities made them feel. Users will also learn the concept of 'up activities' (those that improve their mood) and 'down activities' (those that worsen their mood) and will apply this concept by categorizing their logged activities as either 'up' or 'down'.
- The activity scheduling feature from version 1 will be enhanced by enabling users to 'favorite' their 'up' activities, and subsequently schedule favorited activities as behavioral activations. For example, if a user categorized 'riding my bike' an up activity, then that activity can be favorited and easily scheduled as a behavioral activation.
- Two new tabs in the user interface. A highlights tab that enables users to view summaries of their mood logs, up activities, favorites, and completed activities and associated values. A 'My Logs' tab has also been added that enables users to browse their mood-activity logs and behavioral activations by date.
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### 3.2.3 Release Version 3 (Phase II)

Release version 3 will further expand on version 2 with additional features and content based on product feedback from participants in a recently completed feasibility study of a Spark prototype. Minor modifications may also be made based on feedback from participants who received version 1 or version 2.

Features/content to be added:

- Animations and visual aids to further reinforce psychoeducational content and improve engagement.
- Problem-solving educational content, including how to apply the COPE (Clarity, Options, Perform, Evaluate) problem-solving framework. After learning the framework, users will be guided through an interactive process of applying this framework to overcome obstacles they may encounter when they complete scheduled activities.
- Mindfulness educational content and exercises, including application of mindfulness to mood-activity tracking and scheduled activities to enable users to better notice the relationship between mood and behaviors.
- Relapse prevention education and exercises, including development of a personalized relapse prevention plan. Users will be taught about the possibility of relapse, including potential triggers and early warning signs, and will then identify actions they can take if relapse occurs, including the application of skills that they learned throughout the rest of the program.

### **3.3 Description of the educational control**

#### **3.3.1 Description of educational control for Phase I**

The control mobile application will consist of 5 weeks of psychoeducational content with no active CBT or BA components. Consistent with FDA recommendations, the educational control will be similar to the Limbix Spark program in program duration (5 weeks), amount of content, modality of information delivery (mobile app) and design interface. The educational control will largely be based on the content of the NIMH Teenage Depression e-book (<https://www.nimh.nih.gov/health/publications/teen-depression/index.shtml>). This content will be supplemented with additional content from publicly available government-sponsored websites. Participants will be instructed to complete a weekly Patient Health Questionnaire (PHQ)-8 assessment and participant symptom check in the mobile app.

Program Flow:

- Lesson 1: What is Depression?
  - Description of what depression is, why you can't just "snap out" of it, and what causes depression
  - Additional reading links are provided
- Lesson 2: What are the signs and symptoms of depression?
  - Describes signs and symptoms of depression and addresses the fact that depression may affect different people in different ways
  - Additional reading links provided
- Lesson 3: How do doctors treat depression?
  - Describes psychotherapy and antidepressants
  - Additional reading links provided
- Lesson 4: What else can I do to stay healthy?
  - Describes other activities/healthy habits teens can try to stay healthy as they give treatment time to work
  - Additional readings links provided
- Lesson 5: How do I get help?

- Related resources and links provided
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### **3.3.2 Description of educational control for Phase II**

The control mobile application will consist of 5 weeks of psychoeducational content with no active CBT or BA components. Consistent with FDA recommendations, the educational control will be similar to the Limbix Spark program in program duration (5 weeks), amount of content, modality of information delivery (mobile app) and design interface. The educational control will consist of age-appropriate educational material on the neurobiology of depression. Market research in teens indicated equivalent expectations of treatment benefit for this program when compared to Limbix Spark. Participants will be instructed to complete a weekly Patient Health Questionnaire (PHQ)-8 assessment and participant symptom check in the mobile app.

#### **Program Flow:**

- Lesson 1: Understanding behavior
  - Introduction to program
  - The brain and behavior
  - Studying the brain
  - The teenage brain
- Lesson 2: Exploring the brain
  - Depression in the brain
  - Brain structure
  - Brain function
  - Depression in teens
- Lesson 3: Mastering Messengers
  - Messages in the brains
  - Neurotransmitters
  - Messengers in depression
  - Teens and transmitters
- Lesson 4: Riding the Wave
  - Hormones and behavior
  - Hormones in depression
  - Puberty & the brain
  - Puberty & depression
- Lesson 5: People & personality
  - What are genes?
  - Personality
  - Big 5
  - Big 5 interactive task
  - Genes & depression

### **3.4 Assessments**

Baseline and post-intervention assessments for participants and parents (if under 18) will be completed via a secure web portal. Weekly participant assessments will be completed in the mobile app. Weekly parent assessments will be completed via secure web portal.

## Schedule of Assessments:

|  | Baseline | Weekly during study | Post-intervention |
|--|----------|---------------------|-------------------|
| Patient Health Questionnaire (PHQ-8)                   | X        | X                   | X                 |
| Baseline Questionnaire- Participant                    | X        |                     |                   |
| Baseline Questionnaire- Parent                         | X        |                     |                   |
| Brief Resilience Scale                                 | X        |                     |                   |
| Generalized Anxiety Disorder (GAD-7)                   | X        |                     | X                 |
| PROMIS Pediatric Global Health Scale                   | X        |                     | X                 |
| PROMIS Parent Proxy Global Health Scale                | X        |                     | X                 |
| Mood and Feelings Questionnaire (Short Parent Version) | X        |                     | X                 |
| Participant Symptom Check- Participant                 |          | X                   |                   |
| Participant Symptom Check- Parent                      |          | X                   |                   |
| Post Program Questionnaire- Participant                |          |                     | X                 |
| Post Program Questionnaire- Parent                     |          |                     | X                 |
| System Usability Scale                                 |          |                     | X                 |
| User Engagement Scale                                  |          |                     | X                 |

## Description of Assessments

- The **Patient Health Questionnaire (PHQ-8)** is an 8-item self-report measure for screening for depression and for establishing depression severity. The PHQ-8 has been demonstrated to have high sensitivity and specificity in both adolescents and young adults. Clinically significant improvement is defined as a reduction in assessment score  $\geq 5$ . Post-intervention scores  $< 10$  are defined as remission.
- **Baseline Questionnaire- Participant and Parent:** Contains demographic, clinical history questions, and questions related to the impact of COVID-19.
- The **Brief Resilience Scale** is a 6 item self-report measure for assessing the ability to “bounce back” or recover from stress. It has been shown to be reliable and to measure a unitary construct.
- **7 item Generalized Anxiety Disorder scale (GAD-7).** The GAD-7 is a brief 7-item assessment for generalized anxiety disorder with satisfactory sensitivity and specificity. We will evaluate changes in anxiety symptoms given the high comorbidity between anxiety and depression.

- **PROMIS Pediatric Global Health Scale and PROMIS Parent Proxy Global Health Scale:** The PROMIS Pediatric and Parent Proxy Global 7+2 are 9-item measures that produce essentially a unidimensional measure of global health perception/well-being.
- **Mood and Feelings Questionnaire Short Parent version (MFQ-PS).** The MFQ-PS consists of a series of 13 descriptive phrases regarding how the subject has been feeling or acting recently and is a screening tool for depression in children and young people.
- **Participant Symptom Check- Participant & Parent.** Assesses parent and participant reported clinical concerns, severity level, and relationship of the clinical concern to the intervention.
- **Post-Program Questionnaire- Participant and Parent.** Contains questions about changes in treatment and questions about COVID19
- **System Usability Scale (SUS).** Provides a “quick and dirty”, reliable tool for measuring the usability of systems. It consists of a 10 item questionnaire with five response options for respondents; from Strongly agree to Strongly disagree. The SUS has become an industry standard, with references in over 1300 articles and publications. It is a very easy scale to administer to participants, can be used on small sample sizes with reliable results, and is valid – it can effectively differentiate between usable and unusable systems.
- **User Engagement Scale- Short Form (UES-SF).** A statistically reliable measure of self-reported user engagement. The form has 12 items and uses a 5 point Likert scale.

#### 4. Data Analysis and Data Monitoring

##### 4.1 Primary Outcome

###### Phase I

- Primary outcome measures will include feasibility data including: % of potential participants eligible to participate, % of eligible participants willing to participate, adherence to program (% of enrolled participants completing all sessions by post-treatment), participant satisfaction with the program, and clinical concern rates.

###### Phase II

- Between-subjects treatment-related change in depressive symptoms from baseline to 5-weeks as measured by PHQ-8 for those with baseline PHQ-8  $\geq 10$ .

##### 4.2 Secondary Outcomes/Analyses

###### Phase I

- Between-subjects treatment-related change in depressive symptoms as measured by PHQ-8 for those with baseline PHQ-8  $\geq 5$
- Remission rates based on PHQ-8  $< 10$  (sub-analysis for those with baseline PHQ-8  $\geq 10$ )
- Between-subjects treatment-related change in participant-rated anxiety symptoms and global functioning as measured by GAD-7 and PROMIS Pediatric Global Health Scale
- Between-subjects treatment-related change in parent-reported depressive symptoms and global functioning as measured by MFQ, and PROMIS Parent Proxy Global Health Scale
- Average treatment-related usability (SUS) and engagement (UES-SF) ratings
- Treatment-related program adherence and engagement based on mobile app analytics

###### Phase II

- Remission rates based on PHQ-8 < 10
- Between-group treatment-related differences in participant-rated anxiety symptoms and global functioning as measured by GAD-7 and PROMIS Pediatric Global Health Scale
- Between-group treatment-related differences in parent-reported depressive symptoms and global functioning as measured by MFQ, and PROMIS Parent Proxy Global Health Scale
- Average treatment-related usability (SUS) and engagement (UES-SF) ratings
- Between-group treatment-related differences in clinical concern rates and serious clinical concerns
- Between-group treatment-related differences in program adherence and engagement based on behavioral and mobile app analytics
- 

### 4.3 Tertiary/Exploratory Analyses

#### Phase I

- Exploratory analysis of moderating effects of demographic, clinical, COVID19-specific, and engagement factors on the relationship between treatment status and change in PHQ-8.

#### Phase II

- Exploratory analysis of moderating effects of demographic, clinical, COVID19-specific, resilience (BRS), and engagement factors on the relationship between treatment status and change in PHQ-8.
- Within-group (control group only) treatment-related change in depressive symptoms measured by the PHQ-8.
- Within-group (control group only) treatment related change in participant-rated anxiety symptoms and global functioning as measured by GAD-7 and PROMIS Pediatric Global Health Scale.
- Within-group (control group only) treatment related change in parent-reported depressive symptoms and global functioning as measured by MFQ, and PROMIS Parent Proxy Global Health Scale.
- Within-group (control group only) treatment-related differences in usability (SUS) and engagement (UES-SF) ratings.
- Within-group (control group only) treatment-related differences in clinical concern rates and serious clinical concerns.
- Within-group (control group only) treatment-related differences in program adherence and engagement based on behavioral and mobile app analytics.
- Between-group differences between Spark versions on clinical outcomes (PHQ-8, GAD-7, PROMIS, MFQ), program adherence, usability (SUS) and engagement (UES-SF).
- Factor analysis to investigate whether clusters of symptoms as indicated by PHQ-8 items are differentially impacted by Spark

### 4.4 Data Analysis

#### Phase I

The purpose of Phase I is to evaluate the feasibility of the self-guided Limbix Spark program. Feasibility outcome measures for conducting an RWE fully remote trial of a novel digital treatment for adolescent depression will include enrollment feasibility (i.e., proportion of recruited participants ineligible to participate and/or who decline to enroll), intervention tolerability (i.e., proportion of enrolled participants who discontinue intervention, are lost to follow-up, or experience clinical concerns), and adherence (i.e., proportion of modules completed). Self-report assessments will be collected at pre and post program time points. Weekly PHQ-8 assessments will also be collected during the 5-week intervention as well as at pre and post time points.



Self-reports of clinical concerns will be collected weekly from both the participant and legal guardian (where required) during the 5-week intervention. Patient feedback on ease of use, satisfaction with technology and content, expressed willingness to continue use, and enjoyment will be assessed via questionnaires and a qualitative interview following the intervention. Adherence will be tracked via the mobile app, which will log the time and duration of sessions and user activities.

As per recommendations for pilot studies, formal hypothesis testing will not be prioritized in data analysis<sup>103</sup>. The sample size and planned data analysis, which will rely on qualitative and confidence interval approaches, are appropriate to accomplish the stated objectives of this trial phase. Confidence intervals will be calculated for each outcome measure using varying levels of confidence to evaluate preliminary evidence of effectiveness and feasibility<sup>103</sup>. Feasibility and acceptability of the intervention will also be qualitatively evaluated based on post-intervention interviews with patients. Post-intervention participant interviews are expected to demonstrate that the intervention was feasible for participants to integrate into their daily routine, easy to use, and deemed acceptable and efficacious for helping participants live well with their depression symptoms.

Means, variability, and effect sizes for primary and secondary outcomes will be calculated. A confidence interval approach, using multiple levels of confidence to evaluate the strength of preliminary evidence of efficacy measured by the PHQ-8, will be taken to evaluate whether the mean treatment difference is above zero and whether confidence intervals include a clinically important difference for outcomes. Clinical significance for changes in depressive symptoms will be considered a 5-point reduction in PHQ-8 scores and a post-intervention PHQ-8 score of  $\leq 9$ . For all other measures, clinical significance will be defined as a standardized effect size between 0.3 and 0.5. The time course of weekly PHQ-8 scores will be plotted to assess trends in change over time.

Lastly, we will assess treatment adherence and usability by evaluating program completion and daily mobile app usage, and evaluating means and variability in self-reported usability and engagement using the SUS and UES in the treatment group.

## Phase II

The main purpose of Phase II is to evaluate the effectiveness of the Limbix Spark program relative to an educational control condition. All analyses will be restricted to those participants with PHQ-8  $\geq 10$  unless otherwise indicated. Data from participants who reported a change in their medication or treatment for a mental health disorder that occurred during the study may be excluded from primary analysis. The core analysis strategy in this project is longitudinal mixed effects modeling, where we fully utilize the repeatedly measured primary and secondary outcomes and maximum likelihood estimation will be applied<sup>104</sup>.

Data across versions 2 and 3 will be pooled and statistical analyses conducted with the combined dataset may be computed with version included as a covariate. Statistical analyses may also be conducted separately for versions 2 and 3 cohorts. All analyses will be completed in line with the intent-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. Modern per protocol analyses will also be conducted to estimate treatment effects for participants who adhered to the protocol<sup>105,106,107</sup>. All analysis results will be two-tailed, with a significance level at 0.05 and 95% confidence intervals.

All measures will be analyzed using mixed effects modeling, followed by generalized estimating equations to account for irregularly spaced measurements<sup>108</sup>, fully utilizing all repeated measures and all available data. Missing data will be imputed using multiple imputation and likelihood-based analyses. 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 % missing and whether data are missing at random<sup>109</sup>. Sensitivity analyses will be conducted to determine if data are missing at random. In these analyses, allowing for random intercepts and slopes, the change (slope) will be the key dependent variable and the randomization status will be the key independent variable. The results of these analyses can be easily converted to group or treatment differences at post assessments. In our mixed effects modeling, all variables will be analyzed as continuous with the exception of clinical concerns (occurrence/non-occurrence), which will be treated as a repeatedly measured binary outcome.

As an exploratory investigation, multiple variables will be investigated as possible moderators of treatment effects on depressive symptoms (PHQ-8). For example, we may evaluate medication status, symptom severity, age, sex, COVID19 specific factors, and aspects of program engagement (e.g., time to complete program, duration of use) as potential moderators. For this investigation, we will employ the MacArthur framework for moderator analysis,<sup>110,111</sup> following the eligibility and analytical criteria for determining moderators. To maximize power, moderator analyses will also be conducted using mixed effects modeling.

Exploratory analyses using mixed effects modeling will also be conducted to evaluate whether successive program updates (between versions 2 and 3 of Limbix Spark) result in statistically significant differences on primary and secondary outcome measures, including depressive symptoms, global functioning, and treatment adherence, usability, and engagement.

Content analysis of post-study interviews will be conducted. Data will be codified to identify themes with an emphasis on engagement, usability, comprehension, therapeutic alliance, and overall impact of treatment. Key insights will be drawn from themes and contextualized with quantitative user session data.

Lastly, we will assess treatment adherence by evaluating treatment-related differences in rates of program completion and daily mobile app usage using independent samples (between treatment and control groups) or paired (within the educational control group) t-tests. We will also assess treatment-related differences in self-reported usability and engagement using the SUS and UES scales descriptively by comparing means and variability between groups and within group (control group only)

Statistical analyses for the primary outcome variable and between group differences in rates of clinical concerns rates will be conducted when N=60 (~30/grp) and N=120 (~60/grp) participants have completed Phase II. If no statistical differences are detected in the primary outcome variable, possible moderators of treatment status on the primary outcome may be evaluated, including age, concurrent treatment, and PHQ-8 score at baseline. Results of the interim analyses may be used to adjust recruitment targets for the remainder of the trial.

An effect size will be calculated for the primary outcome and may be used to determine sample size for a Phase III trial.

#### **4.5 Data Monitoring**

This is a low risk research study.

A clinical concern is defined here as any negative experience or symptom reported by participant or parent in the Participant Symptom Check Questionnaire, in freeform text, spontaneously reported, or clinically significant deterioration of symptoms, whether or not thought to be associated with participation in the study.

Clinical concerns will be categorized as follows:

0- Not a clinical concern: Research team determined that triggering event was not a clinical concern

1- Mild clinical concern: Research team determined that triggering event doesn't require clinician input and will continue to monitor participant's responses

2- Moderate clinical concern: Research team determined that triggering event requires clinician input. Clinician determined that research team should continue to monitor participant's responses but that no follow-up was needed.

3- Elevated clinical concern: Research team determined that triggering event requires clinician input. Clinician determined follow-up was indicated and confirmed participant safety (participant did not endorse intent to self harm) via email or phone communication with participant or their parent/guardian or their provider.

4- Significant clinical concern: Research team determined that triggering event requires clinician input. Clinician determined that follow-up was indicated and after follow-up with participant, parent/guardian, or provider determined that participant should be withdrawn from study (e.g. due to suicide attempt, self-harm or self-harm attempt, suicidal ideation with intent, reported hospitalization for self-harm or suicide attempt while enrolled in study).

All adverse device effects and complaints will be recorded (whether anticipated or unanticipated). The project PI and study clinician will determine whether it is in the participant's best interest to remain in the study after any clinical concern.

Anticipated serious clinical concerns, given the study population, include depressive symptoms as defined in the DSM-V, suicidal ideation, active self-harm, clinically significant deterioration in depressive symptoms, suicide attempts, and suicide.

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. Given that the trial intervention is relatively safe and updates to the mobile app are planned a priori, the trial will not be stopped prior to implementation of Spark version 3 for lack of demonstrated efficacy. The trial may be stopped early if PIs, in collaboration with study clinician and DSMB, determine from interim analyses during implementation of version 3 that the Spark app is not efficacious or if there are safety concerns. The trial will be stopped early if PIs, in collaboration with the study clinician, find that the harm to study participants outweighs the benefit of the scientific evidence to be accrued by continuing the trial at any time.

Unanticipated adverse device effects (UADE, 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 of the following criteria:

- Serious
- Associated with the device under investigation
- Unexpected
- Likely to require a significant change to study protocol (i.e., serious clinical concern occurring with a frequency or severity that changes such as modification of safety monitoring protocol or revision of inclusion/exclusion criteria would be required)

PIs will report unanticipated adverse device effects to the IRB and DSMB within 10 working days. Limbix will immediately conduct an evaluation of any reported unanticipated adverse device effect and will report such effects to the FDA within 10 working days. If it is determined that an unanticipated adverse device effect 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 received 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.

Limbix will submit to FDA a copy of any report by an investigator under paragraph (a)(5) of section 21 CFR 812.150 of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

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.

#### **4.5.1 Study Staff Responsibilities**

Data monitoring will be conducted by the research coordinator and overseen by project PIs. In the course of data collection and monitoring, study coordinators will follow an internal safety protocol and alert a study PI or study clinician of any clinical concerns that occur during baseline or post study interview sessions, in freeform text, email/text/phone correspondence, in weekly PHQ scores, and the weekly participant symptom check.

The PIs in consultation with study clinicians will be responsible for monitoring participant safety during the study. The PIs and study clinicians will review relevant assessments, free-responses, and reports from study staff to assess whether it is appropriate for the participant to continue study participation and whether further action to ensure the safety and wellbeing of the participant is warranted. If warranted, the study clinician will reach out to the participant and parent (if under 18) to confirm safety. Because this study is low risk, the study clinicians will not be on call 24/7.

The study clinicians are licensed medical providers and have experience in the assessment of mood and anxiety symptoms, in directing the treatment of such symptoms, and in addressing possible adverse reactions during clinical trials. The study clinicians 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 study clinicians 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.

PIs 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 enrollment of an ineligible participant and failure to obtain informed consent. 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.

#### **4.5.2 Data Safety Monitoring Board**

We will assemble a formal Data and Safety Monitoring Board (DSMB) for Phase II of this study to ensure that the safety of study subjects is protected and that the scientific goals of the study are being met. The assessment of feasibility in Phase I will help to determine what safety parameters are required for Phase II. The team assembled for the DSMB will have relevant and complementary expertise in adolescent psychiatry, clinical trial design, digital health, and statistics. 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.

The DSMB will review and evaluate information relevant to the safety of this study before the implementation of the protocol. Activities of the DSMB will include:

1. Reviewing the study protocol at the start of the study and any proposed amendments related to changes in study design, safety monitoring, or analytic plan.
2. Recommending alterations to the study design
3. Approving the study before commencement
4. Performing expedited monitoring of unexpected adverse device effects at the time of their occurrence and providing recommendations accordingly
5. Performing quarterly review of all clinical concerns
6. Performing ongoing quarterly review of study progress.
7. Reviewing any data that may reflect differences in safety between treatment groups
8. Determining whether study procedures should be changed or the study should be halted for reasons related to the safety of study subjects
9. Performing quarterly review of the completeness and validity of data to be used for analysis of safety and efficacy.

DSMB will convene by video- or teleconference prior to the start of the study and then quarterly through the study period. The Study PIs will be responsible for providing the study protocol to the DSMB prior to the initial meeting. At the initial meeting, the study PIs will meet with the DSMB to review the research protocol, informed consent documents, and plans for data safety and monitoring. The DSMB will review the protocol, discuss with the study team, discuss amongst themselves, and then make recommendations -if any- for modification of the protocol to the study team. The study team will record the recommendations and provide a written document to the DSMB following the meeting for approval and sign off.

The DSMB will then meet on a quarterly basis to assess study progress, data quality, participant recruitment, accrual, and retention, participant risks versus benefits, any breaches of confidentiality, clinical concerns, any interim results of safety and efficacy, and the ethics of this trial. Additional meetings may be convened when

deemed necessary. The study PIs will be responsible for providing a report to the DSMB prior to the meeting with all of the necessary information as outlined above.

The DSMB will provide verbal recommendations during the quarterly meetings related to continuation, termination, or other modifications of the trial and sign off on a written report following the meeting. The DSMB may also conduct independent analysis of the data. The Study PIs will be responsible for providing all data necessary to the DSMB to conduct this analysis. Unexpected serious device effects will be reported to the DSMB within 10 business days.

The IRB will receive a summary report of safety findings on an annual basis from the DSMB. 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 and report clinical concerns are provided with proper and, if necessary, ongoing attention. Any recommendations to improve patient safety, protocol adherence, or data quality will also be included.

## **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, post-study interview audio recordings, and case report forms are 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.

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

The data generated by the Spark mobile client or web portal (used for baseline and post-intervention assessments for participants and parents) 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 research 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 Spark 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 Spark mobile client will be aggregated using Google Analytics. All access to this data will require a valid Limbix employee login for access.

The Spark 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 the study coordinator or PIs 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 research staff may interact with participants to troubleshoot software issues that may arise. Study clinicians may contact participants and/or parents (if under 18) if safety concerns arise.

The research coordinator 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 Spark program at a location of their choice.

No data with subject identifiers will be released, 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 other professionals treating the patient only upon written authorization of the patient. Data will be stored in a confidential manner after the research is completed in accordance with GCP. The PI 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 Sponsor 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. As the 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 if they do not wish to answer a question in the mobile app 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. Participation will be terminated if clinical evidence indicates that continuing would not be in the best interest of the subject as determined by study PI in consultation with a study clinician. 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, determine the best way to mitigate further risks to participant health.

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 data file 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 patient only upon written authorization of the patient. PIs will retain responsibility for ensuring that files are maintained in a secure manner during and after study.

Study personnel will ensure that no individuals outside the research team can overhear conversations during the virtual consent process. 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 treatment 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 in the control arm will receive educational information about depression, including information on healthy habits and wellbeing which may also result in 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.

### **8. Subject Identification, Recruitment and Consent/Assent**

#### **8.1 Method of Subject Identification and Recruitment**

Participants will be recruited via online advertising, social media, word of mouth, flyers, and recommendations by doctors, schools, and other youth and health focused organizations. Providers may be compensated for recruitment efforts (based on hourly effort and not on number of referrals or enrolled participants). Online ads will be targeted to adolescents ages 13-21 or to the parents of adolescents nationwide. Study ads will direct potential participants to a study landing page. The study landing page will provide a basic overview of the study and will ask interested participants to confirm their eligibility based on provided eligibility criteria and set up a virtual consent appointment with a research coordinator. Interested potential participants under 18, when required, will be instructed that they will need a legal guardian to attend the virtual consent appointment.

Flyers and advertisements (provided as attachments) may also be posted online on Craigslist, Facebook, and other websites.

## **8.2 Process of Consent**

Any trained member of the research team will be authorized to obtain informed consent.

Prior to participation, e-consent will be obtained for all participants over 18. For participants under 18, e-consent from a legal guardian and documented assent from participants will be obtained.

The consent process will be 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 explain the study, review the consent form, take time to answer any questions, provide time for decision-making and request an electronic signature.

The session will emphasize:

- 1) This is a research study testing an investigational medical device intended as a treatment for 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
- 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 we must report 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 and assent process will be considered complete only if the adolescent (and legal guardian if the participant is under 18) report comfort with and comprehension of all study procedures. The session will proceed only if informed consent is obtained.

After all questions concerning any aspect of the study have been fully answered by study staff, a Part 11 compliant, electronic signature (via HelloSign) will be obtained from the participant or their legal guardian (if under 18) to document consent. Documentation of the assent of a minor will also be obtained. Participants or their legal guardian 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 form at any time. Signed electronic consent forms will be stored through HelloSign Part 11 compliant services.

If a minor will become of legal consenting age during their participation in the study they will be required to set up an e-consent appointment at that time and consent to continuing their participation.

## **8.3 Subject Capacity**

The study will not enroll participants who are unable to consent or whose legal guardians are unable to consent on their behalf (if potential participants are under 18). Discussions between potential participants and research staff member about study requirements during the consent process will disclose any obvious 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/Representative Comprehension**

All participants will receive a verbal explanation, in terms suited to their comprehension, of the purpose, procedures and potential risks of the study and of their rights as research participants. Participants and their legal guardian will be given ample time and opportunity to carefully review the consent forms and ask questions regarding this study to study staff, family, friends, and/or doctors prior to signing. After expression of understanding, the participants, legal guardian, and research staff member will electronically sign the consent form. Understanding will be confirmed by asking specific questions to patients and their legal guardians to evaluate comprehension.

### **8.5 Debriefing Procedures**

No information will be purposefully withheld from participants or their legal guardians.

### **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 (via HelloSign) will be obtained from the participant or their legal guardian (if under 18) to document consent. Documentation of the assent of a minor will also be obtained. Participants or their legal guardian 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 form at any time. Signed electronic consent forms will be stored through HelloSign 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. 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 \$25 for completing the post-intervention assessments regardless of program adherence. Participants and legal guardians who complete post-intervention user interviews will each be compensated \$25. In Phase II, all participants will also be compensated \$25 for completing baseline assessments and participants randomized to the control arm can earn an additional \$25 for completing a second set of post-intervention assessments after they are provided access to Limbix Spark. Payment will be issued in the form of a gift card upon the completion of the compensated research activity (i.e., completion of assessments or user interview).

## **REFERENCES**

- 1 Patton, G. C. et al. Our future: a Lancet commission on adolescent health and wellbeing. *Lancet* 387, 2423-2478, (2016).
- 2 Keyes, K. M., Gary, D., O'Malley, P. M., Hamilton, A. & Schulenberg, J. Recent increases in depressive symptoms among US adolescents: trends from 1991 to 2018. *Soc Psychiatry Psychiatr Epidemiol* 54, 987-996, (2019).
- 3 Eaton, D. K. et al. Youth risk behavior surveillance - United States, 2009. *MMWR Surveill Summ* 59, 1-142, (2010).
- 4 Shield, B. C. B. Major Depression: The Impact on Overall Health. (2018).

- 5 Mojtabai, R., Olfson, M. & Han, B. National Trends in the Prevalence and Treatment of Depression in Adolescents and Young Adults. *Pediatrics* 138, e20161878, (2016).
- 6 Twenge, J. M., Cooper, A. B., Joiner, T. E., Duffy, M. E. & Binau, S. G. Age, period, and cohort trends in mood disorder indicators and suicide-related outcomes in a nationally representative dataset, 2005–2017. *Journal of abnormal psychology*, (2019).
- 7 Twenge, J. M., Joiner, T. E., Rogers, M. L. & Martin, G. N. Increases in Depressive Symptoms, Suicide-Related Outcomes, and Suicide Rates Among U.S. Adolescents After 2010 and Links to Increased New Media Screen Time. *Clinical Psychological Science* 6, 3-17, (2017).
- 8 Copeland, W. E., Shanahan, L., Costello, E. J. & Angold, A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Archives of general psychiatry* 66, 764-772, (2009).
- 9 Esposito, C. L. & Clum, G. A. Psychiatric symptoms and their relationship to suicidal ideation in a high-risk adolescent community sample. *Journal of the American Academy of Child & Adolescent Psychiatry* 41, 44-51, (2002).
- 10 Keenan-Miller, D., Hammen, C. L. & Brennan, P. A. Health outcomes related to early adolescent depression. *Journal of Adolescent Health* 41, 256-262, (2007).
- 11 Marmorstein, N. R. Longitudinal associations between alcohol problems and depressive symptoms: early adolescence through early adulthood. *Alcoholism: Clinical and Experimental Research* 33, 49-59, (2009).
- 12 McCarty, C. A. et al. Developmental consistency in associations between depressive symptoms and alcohol use in early adolescence. *Journal of studies on alcohol and drugs* 73, 444-453, (2012).
- 13 Ahmedani, B. K., Peterson, E. L., Wells, K. E. & Williams, L. K. Examining the relationship between depression and asthma exacerbations in a prospective follow-up study. *Psychosomatic medicine* 75, 305, (2013).
- 14 Rofey, D. L. et al. A longitudinal study of childhood depression and anxiety in relation to weight gain. *Child psychiatry and human development* 40, 517-526, (2009).
- 15 Thapar, A., Collishaw, S., Pine, D. S. & Thapar, A. K. Depression in adolescence. *Lancet (London, England)* 379, 1056-1067, (2012).
- 16 Weissman, M. M. et al. Depressed adolescents grown up. *Jama* 281, 1707-1713, (1999).
- 17 Fergusson, D. M., Horwood, L. J., Ridder, E. M. & Beautrais, A. L. Subthreshold depression in adolescence and mental health outcomes in adulthood. *Archives of general psychiatry* 62, 66-72, (2005).
- 18 Kim-Cohen, J. et al. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Archives of general psychiatry* 60, 709-717, (2003).
- 19 Bardone, A. M. et al. Adult physical health outcomes of adolescent girls with conduct disorder, depression, and anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry* 37, 594-601, (1998).
- 20 Kessler, R. C. The costs of depression. *Psychiatric Clinics* 35, 1-14, (2012).
- 21 Lynch, F. L. & Clarke, G. N. Estimating the economic burden of depression in children and adolescents. *American journal of preventive medicine* 31, 143-151, (2006).
- 22 Korczak, D. J. & Goldstein, B. I. Childhood Onset Major Depressive Disorder: Course of Illness and Psychiatric Comorbidity in a Community Sample. *The Journal of Pediatrics* 155, 118-123, (2009).
- 23 Birmaher, B., Arbelaez, C. & Brent, D. Vol. 11 619-638 (Elsevier Science, Netherlands, 2002).
- 24 Wisdom, J. P., Clarke, G. N. & Green, C. A. What teens want: barriers to seeking care for depression. *Adm Policy Ment Health* 33, 133-145, (2006).
- 25 Birmaher, B. et al. Childhood and Adolescent Depression: A Review of the Past 10 Years. Part I. *Journal of the American Academy of Child & Adolescent Psychiatry* 35, 1427-1439, (1996).

- 26 Galea, S., Merchant, R. M. & Lurie, N. The Mental Health Consequences of COVID-19 and Physical Distancing: The Need for Prevention and Early Intervention. *JAMA Internal Medicine*, (2020).
- 27 Xiang, Y.-T. et al. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed. *The Lancet Psychiatry* 7, 228-229, (2020).
- 28 Brooks, S. K. et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *The Lancet* 395, 912-920, (2020).
- 29 Federici, S., Bracalenti, M., Meloni, F. & Luciano, J. V. World Health Organization disability assessment schedule 2.0: An international systematic review. *Disability and rehabilitation* 39, 2347-2380, (2017).
- 30 Gulliver, A., Griffiths, K. M. & Christensen, H. Perceived barriers and facilitators to mental health help-seeking in young people: a systematic review. *BMC psychiatry* 10, 113, (2010).
- 31 Rickwood, D., Deane, F. P., Wilson, C. J. & Ciarrochi, J. Young people's help-seeking for mental health problems. *Australian e-journal for the Advancement of Mental health* 4, 218-251, (2005).
- 32 O'Dea, B., Calear, A. L. & Perry, Y. Is e-health the answer to gaps in adolescent mental health service provision? *Current opinion in psychiatry* 28, 336-342, (2015).
- 33 Sheppard, R., Deane, F. P. & Ciarrochi, J. Unmet need for professional mental health care among adolescents with high psychological distress. *Australian & New Zealand Journal of Psychiatry* 52, 59-67, (2018).
- 34 Cheetham, A. et al. Stigmatising Attitudes Towards Depression and Alcohol Misuse in Young People: Relationships with Help-Seeking Intentions and Behavior. *Adolescent Psychiatry* 9, 24-32, (2019).
- 35 Health, U. S. D. o. & Human, S. (Rockville, MD: National Center for Health Workforce Analysis. Retrieved from ..., 2016).
- 36 Andrilla, C. H. A., Patterson, D. G., Garberson, L. A., Coulthard, C. & Larson, E. H. Geographic variation in the supply of selected behavioral health providers. *American journal of preventive medicine* 54, S199-S207, (2018).
- 37 Cunningham, P. J. Beyond Parity: Primary Care Physicians' Perspectives On Access To Mental Health Care: More PCPs have trouble obtaining mental health services for their patients than have problems getting other specialty services. *Health affairs* 28, w490-w501, (2009).
- 38 Thomas, C. R. & Holzer Iii, C. E. The continuing shortage of child and adolescent psychiatrists. *Journal of the American Academy of Child & Adolescent Psychiatry* 45, 1023-1031, (2006).
- 39 Williams, M. E., Latta, J. & Conversano, P. Eliminating the wait for mental health services. *J Behav Health Serv Res* 35, 107-114, (2008).
- 40 Kowalewski, K., McLennan, J. D. & McGrath, P. J. A preliminary investigation of wait times for child and adolescent mental health services in Canada. *J Can Acad Child Adolesc Psychiatry* 20, 112-119, (2011).
- 41 Schraeder, K. E. & Reid, G. J. Why wait? The effect of wait-times on subsequent help-seeking among families looking for children's mental health services. *J Abnorm Child Psychol* 43, 553-565, (2015).
- 42 Westin, A. M. L., Barksdale, C. L. & Stephan, S. H. The effect of waiting time on youth engagement to evidence based treatments. *Community mental health journal* 50, 221-228, (2014).
- 43 Smith, D. H., Hadorn, D. C. & Steering Committee of The Western Canada Waiting List, P. Lining up for children's mental health services: a tool for prioritizing waiting lists. *J Am Acad Child Adolesc Psychiatry* 41, 367-376; discussion 376-367, (2002).
- 44 Biringer, E., Sundfjør, B., Davidson, L., Hartveit, M. & Borg, M. Life on a waiting list: How do people experience and cope with delayed access to a community mental health center? *Scandinavian Psychologist* 2, (2015).
- 45 Abuse, S. Mental Health Services Administration.(2017). Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health (HHS

- Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality. Substance Abuse and Mental Health Services Administration. Retrieved from <https://www.samhsa.gov/data>, (2018).
- 46 Kataoka, S. H., Zhang, L. & Wells, K. B. Unmet need for mental health care among U.S. children: variation by ethnicity and insurance status. *Am J Psychiatry* 159, 1548-1555, (2002).
- 47 Gunnell, D. et al. Suicide risk and prevention during the COVID-19 pandemic. *The Lancet Psychiatry*, (2020).
- 48 Orben, A., Tomova, L. & Blakemore, S.-J. The effects of social deprivation on adolescent social development and mental health. (2020).
- 49 Zuckerbrot, R. A. et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): part I. Practice preparation, identification, assessment, and initial management. *Pediatrics* 141, e20174081, (2018).
- 50 Jureidini, J. N. et al. Efficacy and safety of antidepressants for children and adolescents. *Bmj* 328, 879-883, (2004).
- 51 Cipriani, A. et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *The Lancet* 388, 881-890, (2016).
- 52 DeBar, L. L., Clarke, G. N., O'Connor, E. & Nichols, G. A. Treated prevalence, incidence, and pharmacotherapy of child and adolescent mood disorders in an HMO. *Mental Health Services Research* 3, 73-89, (2001).
- 53 Cheung, A. H., Emslie, G. J. & Mayes, T. L. Review of the efficacy and safety of antidepressants in youth depression. *Journal of Child Psychology and Psychiatry* 46, 735-754, (2005).
- 54 Whittington, C. J. et al. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *The Lancet* 363, 1341-1345, (2004).
- 55 Stafford, A. M. et al. The Natural Course of Adolescent Depression Treatment in the Primary Care Setting. *Journal of Pediatric Health Care* 34, 38-46, (2020).
- 56 O'Connor, B. C. et al. Usual care for adolescent depression from symptom identification through treatment initiation. *JAMA pediatrics* 170, 373-380, (2016).
- 57 Powell, A. C., Chen, M. & Thammachart, C. The Economic Benefits of Mobile Apps for Mental Health and Telepsychiatry Services When Used by Adolescents. *Child Adolesc Psychiatr Clin N Am* 26, 125-133, (2017).
- 58 Pennant, M. E. et al. Computerised therapies for anxiety and depression in children and young people: a systematic review and meta-analysis. *Behav Res Ther* 67, 1-18, (2015).
- 59 Hollis, C. et al. Annual Research Review: Digital health interventions for children and young people with mental health problems – a systematic and meta-review. *Journal of Child Psychology and Psychiatry* 58, 474-503, (2017).
- 60 Irvine, M. More youth use smartphones as route to Web. (Chicago, 2014).
- 61 Montague, A. E., Varcin, K. J., Simmons, M. B. & Parker, A. G. Putting technology into youth mental health practice: young people's perspectives. *Sage Open* 5, 2158244015581019, (2015).
- 62 Fein, J. A. et al. Feasibility and effects of a web-based adolescent psychiatric assessment administered by clinical staff in the pediatric emergency department. *Archives of pediatrics & adolescent medicine* 164, 1112-1117, (2010).
- 63 Gardner, W. et al. Screening, triage, and referral of patients who report suicidal thought during a primary care visit. *Pediatrics* 125, 945-952, (2010).
- 64 Bradford, S. & Rickwood, D. Acceptability and utility of an electronic psychosocial assessment (myAssessment) to increase self-disclosure in youth mental healthcare: a quasi-experimental study. *BMC psychiatry* 15, 305, (2015).

- 65 Scott, M. A. et al. School-based screening to identify at-risk students not already known to school professionals: the Columbia suicide screen. *American Journal of Public Health* 99, 334-339, (2009).
- 66 Cho, H.-W. A Long Journey Back to Normal Life. *Osong Public Health and Research Perspectives* 11, 65, (2020).
- 67 World Health, O. (2005).
- 68 Liu, S. et al. Online mental health services in China during the COVID-19 outbreak. *The Lancet Psychiatry* 7, e17-e18, (2020).
- 69 Torous, J., Myrick, K. J., Rauseo-Ricupero, N. & Firth, J. Digital Mental Health and COVID-19: Using Technology Today to Accelerate the Curve on Access and Quality Tomorrow. *JMIR mental health* 7, e18848, (2020).
- 70 Vibhakar, V., Allen, L. R., Gee, B. & Meiser-Stedman, R. A systematic review and meta-analysis on the prevalence of depression in children and adolescents after exposure to trauma. *Journal of affective disorders*, (2019).
- 71 Burke, A. R., McCormick, C. M., Pellis, S. M. & Lukkes, J. L. Impact of adolescent social experiences on behavior and neural circuits implicated in mental illnesses. *Neuroscience & Biobehavioral Reviews* 76, 280-300, (2017).
- 72 Beardslee, W. R., Gladstone, T. R. G. & O'Connor, E. E. Developmental risk of depression: experience matters. *Child and Adolescent Psychiatric Clinics* 21, 261-278, (2012).
- 73 Luyten, P. & Fonagy, P. The stress–reward–mentalizing model of depression: An integrative developmental cascade approach to child and adolescent depressive disorder based on the Research Domain Criteria (RDoC) approach. *Clinical psychology review* 64, 87-98, (2018).
- 74 Henje Blom, E. et al. The neuroscience and context of adolescent depression. *Acta Paediatrica* 105, 358-365, (2016).
- 75 Brooks, S. K. et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *The Lancet*, (2020).
- 76 Compton, S. N. et al. Cognitive-behavioral psychotherapy for anxiety and depressive disorders in children and adolescents: an evidence-based medicine review. *Journal of the American Academy of Child & Adolescent Psychiatry* 43, 930-959, (2004).
- 77 National Collaborating Centre for Mental, H. (British Psychological Society).
- 78 Hofmann, S. G., Asnaani, A., Vonk, I. J., Sawyer, A. T. & Fang, A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. *Cognit Ther Res* 36, 427-440, (2012).
- 79 Yang, L. et al. Efficacy and acceptability of cognitive behavioral therapy for depression in children: A systematic review and meta-analysis. *Academic pediatrics* 17, 9-16, (2017).
- 80 Hetrick, S. E., Cox, G. R., Witt, K. G., Bir, J. J. & Merry, S. N. Cognitive behavioural therapy (CBT), third-wave CBT and interpersonal therapy (IPT) based interventions for preventing depression in children and adolescents. *Cochrane Database of Systematic Reviews*, (2016).
- 81 Clarke, G. et al. Cognitive behavioral therapy in primary care for youth declining antidepressants: a randomized trial. *Pediatrics* 137, e20151851, (2016).
- 82 Hofmann, S. G., Asnaani, A., Vonk, I. J. J., Sawyer, A. T. & Fang, A. The efficacy of cognitive behavioral therapy: A review of meta-analyses. *Cognitive therapy and research* 36, 427-440, (2012).
- 83 Ebert, D. D. et al. Internet and Computer-Based Cognitive Behavioral Therapy for Anxiety and Depression in Youth: A Meta-Analysis of Randomized Controlled Outcome Trials. *PLOS ONE* 10, e0119895, (2015).
- 84 Kanter, J. W. et al. What is behavioral activation? A review of the empirical literature. *Clin Psychol Rev* 30, 608-620, (2010).

- 85 Lejuez, C. W., Hopko, D. R., Acierno, R., Daughters, S. B. & Pagoto, S. L. Ten year revision of the brief behavioral activation treatment for depression: revised treatment manual. *Behav Modif* 35, 111-161, (2011).
- 86 Pass, L., Lejuez, C. W. & Reynolds, S. Brief Behavioural Activation (Brief BA) for Adolescent Depression: A Pilot Study. *Behav Cogn Psychother* 46, 182-194, (2018).
- 87 McCauley, E. et al. The Adolescent Behavioral Activation Program: Adapting Behavioral Activation as a Treatment for Depression in Adolescence. *J Clin Child Adolesc Psychol* 45, 291-304, (2016).
- 88 Pass, L., Hodgson, E., Whitney, H. & Reynolds, S. Brief Behavioral Activation Treatment for Depressed Adolescents Delivered by Nonspecialist Clinicians: A Case Illustration. *Cognitive and Behavioral Practice* 25, 208-224, (2018).
- 89 Davey, C. G., Yucel, M. & Allen, N. B. The emergence of depression in adolescence: development of the prefrontal cortex and the representation of reward. *Neurosci Biobehav Rev* 32, 1-19, (2008).
- 90 Forbes, E. E. et al. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am J Psychiatry* 166, 64-73, (2009).
- 91 National Collaborating Centre for Mental, H. in Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet] (Centre for Reviews and Dissemination (UK), 2005).
- 92 Chu, B. C., Colognori, D., Weissman, A. S. & Bannon, K. Vol. 16 408-419 (Elsevier Science, Netherlands, 2009).
- 93 Jacob, M., L. Keeley, M., Ritschel, L. & Craighead, W. E. Behavioural activation for the treatment of low-income, African American adolescents with major depressive disorder: a case series. *Clinical Psychology & Psychotherapy* 20, 87-96, (2013).
- 94 Ritschel, L., L. Ramirez, C., Jones, M. & Edward Craighead, W. Behavioral Activation for Depressed Teens: A Pilot Study. *Cognitive and Behavioral Practice* 18, 281-299, (2011).
- 95 Oud, M. et al. Effectiveness of CBT for children and adolescents with depression: A systematic review and meta-regression analysis. *Eur Psychiatry* 57, 33-45, (2019).
- 96 Webb, C. A. et al. Cognitive versus behavioral skills in CBT for depressed adolescents: Disaggregating within-patient versus between-patient effects on symptom change. *J Consult Clin Psychol* 87, 484-490, (2019).
- 97 Rooksby, M., Elouafkaoui, P., Humphris, G., Clarkson, J. & Freeman, R. Internet-assisted delivery of cognitive behavioural therapy (CBT) for childhood anxiety: Systematic review and meta-analysis. *Journal of Anxiety Disorders* 29, 83-92, (2015).
- 98 Grist, R., Croker, A., Denne, M. & Stallard, P. Technology Delivered Interventions for Depression and Anxiety in Children and Adolescents: A Systematic Review and Meta-analysis. *Clin Child Fam Psychol Rev* 22, 147-171, (2019).
- 99 Huguet, A. et al. A Systematic Review of Cognitive Behavioral Therapy and Behavioral Activation Apps for Depression. *PLoS One* 11, e0154248, (2016).
- 100 Karyotaki, E. et al. Efficacy of Self-Guided Internet-Based Cognitive Behavioral Therapy in the Treatment of Depressive Symptoms. *JAMA Psychiatry* 74, 351-359, (2017).
- 101 Davies, E. B., Morriss, R., & Glazebrook C. Computer-Delivered and Web-Based Interventions to Improve Depression, Anxiety, and Psychological Well-Being of University Students: A Systematic Review and Meta-Analysis. *J Med Internet Res* 16, e130, (2014).
- 102 Grist, R., Croker, A., Denne, M., & Stallard, P. Technology Delivered Interventions for Depression and Anxiety in Children and Adolescents: A Systematic Review and Meta-analysis. *Clin Child Fam Psychol Rev* 22, 147-171 (2019).
- 103 Lee, E. C., et al. The statistical interpretation of pilot trials: should significance thresholds be reconsidered?. *BMC Medical Research Methodology*. 14:41, (2014).



- 104 Bates, D., Mächler, M., Bolker, B. & Walker, S. Fitting linear mixed-effects models using lme4. arXiv preprint arXiv:1406.5823, (2014).
- 105 Jo, B. Estimation of intervention effects with noncompliance: Alternative model specifications. *Journal of Educational and Behavioral Statistics* 27, 385-409, (2002).
- 106 Jo, B., Ginexi, E. M. & Ialongo, N. S. Handling missing data in randomized experiments with noncompliance. *Prevention Science* 11, 384-396, (2010).
- 107 Stuart, E. A. & Jo, B. Assessing the sensitivity of methods for estimating principal causal effects. *Statistical methods in medical research* 24, 657-674, (2015).
- 108 Garcia, T. P., & Marder, K., Statistical Approaches to Longitudinal Data Analysis in Neurodegenerative Diseases: Huntington's Disease as a Model, *Curr Neurol Neurosci Rep* 17(2): 14, (2017).
- 109 Jakobsen, J.C., et al. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Med Res Methodol* 17: 162, (2017).
- 110 Kraemer, H. C., Wilson, G. T., Fairburn, C. G. & Agras, W. S. Mediators and moderators of treatment effects in randomized clinical trials. *Archives of general psychiatry* 59, 877-883, (2002).
- 111 Kraemer, H. C, Kiernan, M., Essex, M. & Kupfer, D. J. How and why criteria defining moderators and mediators differ between the Baron & Kenny and MacArthur approaches. *Health Psychology* 27, S101, (2008).