Woebot Health

W-GenZD-003: Reframe Study

A Randomized Controlled Trial of the Feasibility and Acceptability of W-GenZD versus CBT-lite teletherapy for Adolescents seeking Mental Health Services

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Protocol Version and Amendment Tracking

Version Number/Amendment	Approval Date
1.0	03/31/2022
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Table 1. Schedule of Events

Visit Weeks/Days	Screening Period		Treatment Period			Follow-Up Period	
	Screening Day -7 to -1	*Baseline Day 0*	*Visit 2 Day 5 (+2)*	*Visit 3/Week 2 Day 14(+6)*	*Visit 4/ Week 4 (EOT) Day 28 (+6)*	*Visit 5/ Week 6 Day 42 (+6)*	*Visit 6 Week 8 (EOS) Day 56 (+6)*
Informed Consent/Assent	X						
Demographics [c, d]	X						
Psychiatric History [c, d]	X						
Prior & Concomitant Medications/Therapy [d]	X				X		
CHKD Brief Clinical Needs Assessment Information [d]	X						
Eligibility Confirmation (Inclusion/Exclusion)	X						
Randomization		X					
Download Study Application [a]		X					
PHQ-8 [b]		X		X	X		X
GAD-7 [b]		X			X		X
MFQ [b]		X			X		X
WAI-SR [b]			X		X		
CSQ-8 [b]					X		
Satisfaction Questionnaire [a]					X		
UPRI [b]					X		
App Engagement Metrics (W-GenZD only)					X		
Weekly teletherapy Group Attendance (CBT-lite only)[d]			X				
Parental Check-Ins (Telephonic)				X	X	X	X
SNP/Safety Response [e]	X						
Healthcare Utilization [c, d]							X
Assessment of AE/SAEs				X	X	X	X
Termination of W-GenZD and Teletherapy Access					X		
Participant and Parent/Guardian Exit Interviews [f]							X

[a] W-GenZD participants only, [b] Self-Report Clinical Assessment (adolescent), [c] Parent/Guardian Questionnaire, [d] Collected from CHKD system, [e] A SNP or Safety event will trigger an unscheduled visit from ICF to EOS, see section 5.6, [f] Optional study procedure; EOS = End of Study; EOT = End of Treatment; SNP=Safety Net Protocol

Protocol Synopsis

Study Device	W-GenZD
Protocol Number:	W-GenZD-003
Protocol Title:	A Randomized Controlled Trial of the Feasibility and Acceptability of W-GenZD versus CBT-lite teletherapy for Adolescents seeking Mental Health Services
Main Criteria for Inclusion:	**Inclusion** 1. Have completed triage at CHKD and have been deemed appropriate for the low-intensity intervention track, given presenting problem(s) of depressive or anxiety symptoms 2. Adolescent 13-17 years of age, inclusive 3. U.S. Resident 4. Both adolescent participant and parent/guardian are able to read and write in English 5. Own or have regular access to a smartphone (Android or iOS smartphone with a recent, supported operating system), that can receive SMS messages, and reliable Wi-Fi access or sufficient data to engage with assigned treatment condition for the duration of the study 6. If currently prescribed antidepressant medications (e.g. escitalopram/Lexapro, fluoxetine/ Prozac), antipsychotic medications (e.g. aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, risperidone), or stimulants (e.g. amphetamine/Adderall, Methylphenidate/Ritalin) and alpha agonists (e.g. atomoxetine/Strattera, Guanfacine/Intuniv) they are at a regular, stable dose for at least 60 days at screening 7. Not currently actively engaged is psychotherapy 8. Available and committed to engage with the program and complete assessments for a 8-week duration. 9. Family is willing and able to engage in discussion of safety planning in the event of suicidal symptoms

	Exclusion 1. Lifetime diagnosis of a psychotic disorder (including schizophrenia or schizoaffective disorder) 2. Lifetime diagnosis of bipolar disorder 3. Lifetime diagnosis of autism spectrum disorder or pervasive developmental disorder (e.g. autism, Asperger syndrome, Rett's syndrome) 4. Current diagnosis of developmental delay or intellectual disability 5. Suicidal ideation with a plan or intent or a suicidal attempt within the past 12 months 6. History of (a) drug and/or alcohol abuse within the past 12 months 7. Current use of benzodiazepines (e.g. lorazepam, clonazepam, alprazolam, diazepam, triazolam) or certain sleep aids (zolpidem, eszopiclone, zaleplon) 8. Previous Woebot application use 9. Enrollment of more than one member of the same household
Study Primary Objective:	What is the feasibility and acceptability of W-GenZD among a group of adolescents and who have been screened and triaged into low-intensity treatment within CHKD?
Study Design:	This study will be a randomized controlled trial of W-GenZD versus fcpton The trial will consist of 3 primary phases: Screening/Baseline, Treatment, and a Follow-up period.
Treatment Regimen:	W-GenZD: 5-10 minutes of daily use recommended Teletherapy CBT Groups: 1 group/week of treatment period
Duration of Study Participation:	8 weeks
Number of Participants:	260 participants
Number of Sites:	1
Primary Endpoints:	Primary Feasibility and Acceptability outcomes at 4-weeks: ● Usage Rating Profile Intervention (URPI)-Feasibility and URPI-Acceptability ● Client Satisfaction Questionnaire (CSQ-8) Additional feasibility and acceptability metrics:

	● App engagement metrics (W-GenZD condition) ● Content/Program satisfaction ratings (both conditions) ● Group attendance (CBT-lite teletherapy condition) Qualitative findings about the participant experience, based on interviews with a self-selected subset of participants (adolescent and parent/guardian)
Secondary Endpoints:	● Patient Health Questionnaire for Teens (PHQ-8) total score ● Generalized Anxiety Disorder Questionnaire (GAD-7) ● Mood and Feeling Questionnaire (MFQ)
Tertiary Endpoint:	● Working Alliance Inventory-SR (WAI-SR)
Exploratory Endpoints:	● To observe and describe the utilization and outcomes of the safety procedures utilized within this study (Safety Net Protocol, AE/SAEs and device relatedness) ● Pre-period and study-period healthcare utilization data. This will include: ○ Diagnosis (e.g., ICD code) and service rendered (e.g., CPT code) ○ Emergency Department utilization ○ Primary care utilization (e.g., primary care well visit and sick visit appointment) ○ Behavioral-health related utilization (psychiatry, psychology, other therapist, etc) ○ Psychiatric medication prescriptions ○ Social determinants of health information (e.g., food and housing insecurity and social work utilization) ○ Comorbidity data (i.e., any additional behavioral health or physical health diagnoses) ○ Problem List ○ Any relevant lifetime psychiatric assessments (e.g., Vanderbilt, PHQ)
Interim Report:	Readout of complete baseline sample descriptive stats (demographics, enrollment data, etc) and baseline scores of measures

1. Introduction

1.1 Background

Adolescence is a *unique and critical period* of neurological development. The brain will never be as sensitive to reward nor as plastic as it is during adolescence [1]. It is also the peak time for the onset of most mental illnesses [2]. Mental illnesses that emerge before adulthood carry a 10-fold higher cost than those that emerge in adulthood [3]. With mental illness being the largest and most costly problem to the global economy [4] and depression specifically being the leading cause of disability worldwide [5], the public health impacts are staggering, yet persistently increasing, especially among adolescents [6]. Adolescence is a very vulnerable developmental life stage, in which 50% of lifetime cases of mental illness begin by the age of 14, and 75% by the age of 24 [7]. Depression onset in adolescence also confers high risk for chronic depression recurrence as well as other psychiatric sequelae [8,9].

The American Psychological Association's (APA) [10], American Academy of Pediatrics (AAP) [8], American Academy of Child and Adolescent Psychiatry (AACP), and the National Institutes of Clinical Excellence's (NICE)[11] agree that swift and early intervention of depression in adolescence is a critical part of the standard of care for this population, with all recommending routine screening for depression, particularly in primary care settings [8]. Standard of care treatment recommendations across the board include psychotherapy and/or pharmacotherapy, with APA, AAP and NICE unanimously recommending cognitive behavioral therapy (CBT) and interpersonal therapy for adolescents (IPT-A) as the most evidence-based psychotherapeutic options. Data suggest that combining psychotherapy and an antidepressant medication, particularly for more complicated or severe presentations, may have better outcomes than either treatment alone [12, 13]. Additionally, support in the form of psychoeducation and case management, as well as involvement of family and school throughout the treatment period is also recommended [8, 14, 15].

In practice, there are barriers to implementing these recommendations consistently and thus, as many as two out of three adolescents with depression *do not receive any treatment* [13]. There are only two FDA-approved psychopharmacological options for adolescent MDD, compounded by a dearth of high-quality empirical evidence compared to adult MDD and the potential for serious side effects. Critically, lack of access is consistently a treatment barrier for many adolescents, especially access to clinicians skilled in high-quality psychotherapy and/or pharmacotherapy. This longstanding national shortage of child and adolescent specialty trained providers [13] often leaves the complex management of adolescent depression in the overburdened hands of primary care providers. In addition, many families are reluctant to consider antidepressant medications as first-line treatment for adolescents [16], preferring psychotherapy [17]. Yet, research shows that recommended psychotherapies are seldom used [18, 19]. Persistent barriers to use pertain to access, cost and stigma [11, 20], with the latter discouraging adolescents from seeking help. Additional problems in real-world practice include incomplete use of screening tools even when recommended at the organizational level within a pediatric care network [21], limited guidance on how a clinician should use those routine assessments to inform treatment decisions [22] and concerning racial disparities in rates of treatment and follow-up [23].

Clearly, early and successful intervention is crucial, and yet there have been surprisingly few therapeutic approaches *specifically designed for adolescents*. Up to 75% of young people will never get the care that they need [24] and early dropout is common among those that do [25], suggesting that the structure and systems of traditional clinical settings are ill fitted to adolescent lives. In short, access, broadly defined, remains the most significant barrier to mental health care for young people.

Undoubtedly technology must become part of the solution, as part of an ecosystem of mental health services. However, presently there are no FDA-approved mobile medical devices for the treatment of major depression in adolescence.

1.2 Clinical Experience with Woebot

Woebot is an automated relational agent based on the most researched and scientifically validated psychotherapies, primarily CBT, and accessible via an iOS and Android application. The user experience is centered around mood tracking and goal-oriented, tailored conversations. Users become familiar with Woebot as a friendly, helpful character that is explicitly not a human, nor a therapist. Woebot has been designed with a personality to facilitate a working alliance over time. Daily push-notifications prompt users to check-in with Woebot. Upon opening the app, Woebot asks users what they are doing (context) and how they are feeling (mood). Using proprietary natural language processing (NLP) and artificial intelligence (AI), Woebot is able to understand users in an organic, familiar way and lead them appropriately through a program that is personalized each day, in real-time, to the user's needs.

1.2.1 Randomized Controlled Trial (RCT) of an Early Prototype of W-GenZD in 18-28 year olds

Purpose: To evaluate the feasibility, acceptability, and preliminary efficacy of W-GenZD among a college-based sample (N=70) in an RCT comparing an early prototype of W-GenZD to an information-only control group.

Methods: Participants ages 18-28 years (N = 70) who self-identified as experiencing symptoms of depression and anxiety were randomized to receive Woebot or an e-book on depression published by the National Institute of Mental Health. Outcomes were assessed at 2-weeks end-of-treatment. The study was approved by the Stanford University IRB and published in the Journal of Medical Internet Research (JMIR) [26]. The study was powered for the full 18-28 age range. A post-hoc subgroup analysis was also performed among those participants aged 18-21 years (n=26) to characterize clinical outcomes for this relevant age group specifically.

Key Results: In the broader cohort of all participants ages 18-28 years, those in the Woebot group significantly (F=6.5; p=.01) reduced their symptoms of depression over the study period as measured by the Patient Health Questionnaire (PHQ-9), relative to those in the control group [26]. Participants engaged with the device an average of 12.14 times (SD=2.23; median=12; range 8-18) over the 2-week study period. As it relates specifically to the subgroup of interest, 37% of participants (n=26/70) were ages 18-21 years. Intent-to-treat analysis indicated that Woebot participants ages 18-21 years experienced a reduction in symptoms of depression as measured by the PHQ-9 (mean reduction = 1.7, SD (4.2)), and in symptoms of anxiety as measured by the Generalized Anxiety Disorder (GAD-7) scale (mean reduction = 1.7, SD (3.2)) at 2-weeks, as compared to baseline. Within-subject effect sizes on both measures were small to medium (Cohen's d = .27 and .31 for PHQ-9 and GAD-7, respectively); neither of these differences was statistically significant (t = -1.9, p = .09 and t = -1.4, p = 0.19, respectively) at 2-weeks, relative to baseline, due the limited sample size as the original study was powered for the full 18-28 range. However, the subgroup results show a trend that is consistent with the overall results.

Conclusion: RCT results indicated that W-GenZD was a feasible, effective, and engaging way to digitally deliver CBT to participants self-identifying as having symptoms of depression or anxiety, in the adolescent population ages 18-28. Results in the 18-21 subgroup were consistent with those in the larger study, but were not statistically significant since the study was originally powered for the larger group.

1.3 Rationale

In recent years, there has been an explosion of interest and development of technological solutions to either supplement existing mental health treatments or expand access to quality mental health services. This development was matched by patient demand with about 70% showing interest in using mobile applications (apps) to self-monitor and self-manage their mental health [1]. Internet interventions for anxiety and depression have significant empirical support [2] with outcomes comparable to therapist-delivered cognitive behavioral therapy (CBT) [3-4]. Yet, despite demonstrated efficacy, they are characterized by relatively poor adoption and adherence. One review found a median minimal completion rate (usually defined as completion of ~4 sessions) of 56% [5].

Another problem is that almost all of the research on mobile apps was conducted on apps that are not commercially available. For example, one systematic review of 5,464 abstracts identified just 5 apps that had supporting evidence from randomized controlled trials, and none of them were available commercially [6]. In contrast, apps that were commercially available typically lack evidence and/or a commitment to demonstrate outcomes.

Conversational agents, or chatbots, are software programs that use natural language as inputs and outputs instead of, for instance, menu commands (e.g., File/Save As…) or graphical inputs (e.g., clicking on an icon to open an app). Recent advancements in voice recognition have given rise to the emergence of many conversational agents such as Apple's Siri or Amazon's Alexa. Interacting in this way appears to be a more natural medium through which individuals engage with technology. People respond and converse with nonhuman agents in ways that mirror emotional and social discourse dynamics when discussing behavioral health [7].

Moreover, evidence-based in-person therapies such as CBT, traditionally assign clients opportunities to practice therapy skills outside of sessions, commonly referred to as therapy homework. Historically, it's often proven difficult to engage CBT clients in their homework on a regular basis. Conversational interfaces redefine the entire concept of therapy homework; their ability to be available in the actual moment of need, regardless of time of day or day of week, allows clients to engage with their therapy skills in-vivo, when it matters most.

Children's Hospital of the King's Daughters (CHKD) is a 206-bed, freestanding children's hospital and the heart of an integrated pediatric health care system with roughly 5,000 admissions to the hospital every year. The CHKD mental health program is organized as a stepped care model in which patients are triaged into either low or high-intensity tracks depending on the severity of symptoms, treatment history, and clinical presentation. Due to the demand for adolescent mental health services, the wait time to connect with providers is currently around 3 months. During this waiting period, CHKD offers several teletherapy groups to adolescents and their families seeking services as a support that can be utilized until there is availability.

This protocol aims to demonstrate that Woebot, specifically W-GenZD, is a viable option for this type of healthcare ecosystem.

2. Objectives

Primary Aim: What is the feasibility and acceptability of W-GenZD among a group of adolescents and who have been screened and triaged into low-intensity treatment within CHKD?

- Primary Feasibility and Acceptability outcomes at 4-weeks:
    - Usage Rating Profile Intervention (URPI)-Feasibility and URPI-Acceptability

    - Client Satisfaction Questionnaire (CSQ-8)
- Additional feasibility and acceptability metrics:
    - App engagement metrics (W-GenZD condition)
    - Content/Program satisfaction ratings (both conditions)
    - Group attendance (CBT-lite teletherapy condition)
- Qualitative findings about the participant experience, based on interviews with a self-selected subset of participants (adolescent and parent/guardian)

Secondary Aim: What is the preliminary comparative efficacy of W-GenZD and CBT-lite telehealth zoom groups to manage mood concerns at 4-weeks end of treatment (EOT), relative to baseline?

- Secondary outcomes:
    - Patient Health Questionnaire for Teens (PHQ-8) total score

Tertiary Aim: Investigate potential between group differences on Working Alliance.

- Tertiary outcomes:
    - Working Alliance Inventory-SR (WAI-SR)
    - Generalized Anxiety Disorder Questionnaire (GAD-7)
    - Mood and Feeling Questionnaire (MFQ)

Exploratory Aim: To observe and describe the utilization and outcomes of the safety procedures utilized within this study (Safety Net Protocol, AE/SAEs and device relatedness). To describe the sample population with respect to healthcare utilization, social determinants of health, and comorbidity data for pre-study and during-study (treatment and follow-up) periods and examine associations between these factors and study clinical, alliance, engagement and satisfaction outcomes.

3. Study Population

3.1 Selection of Study Population

Participants are children referred to the CHKD mental health program and are eligible for the low-intensity intervention track. Approximately 30 adolescents are triaged into this low-intensity track per week. In order to be eligible for the low-intensity track, adolescents must *not* meet one or more of the following criteria: have had suicidal ideation within the last 2 weeks or be a current risk to self/others, psychotic presentation, meet criteria for an active eating disorder, history of mania, substance use disorder is the primary clinical problem, is at imminent risk of expulsion, or is currently prescribed 4 or more psychotropic medications.

A minimum of 260 participants (approximately 130 participants/arm) will be enrolled. If participants meet all of the following inclusion criteria and none of the exclusion criteria, they will be randomly assigned to study treatment.

3.1.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Have been referred to CHKD Mental Health Program and deemed appropriate for the low-intensity intervention track, given presenting problem(s) of depressive or anxiety symptoms
2. Adolescent 13-17 years of age, inclusive
3. U.S. Resident

4. Both adolescent participant and parent/guardian are able to read and write in English
5. Own or have regular access to a smartphone (Android or iOS smartphone with a recent, supported operating system), that can receive SMS messages, and reliable Wi-Fi access or sufficient data to engage with assigned treatment condition for the duration of the study
6. If currently prescribed antidepressant medications (e.g. escitalopram/Lexapro, fluoxetine/ Prozac), antipsychotic medications (e.g. aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, risperidone), or stimulants (e.g. amphetamine/Adderall, Methylphenidate/Ritalin) and alpha agonists (e.g. atomoxetine/Strattera, Guanfacine/Intuniv) they are at a regular, stable dose for at least 60 days at screening
7. Not currently actively engaged in psychotherapy
8. Available and committed to engage with the program and complete assessments for a 8-week duration.
9. Family is willing and able to engage in discussion of safety planning in the event of suicidal symptoms

3.1.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Lifetime diagnosis of a psychotic disorder (including schizophrenia or schizoaffective disorder)
2. Lifetime diagnosis of bipolar disorder
3. Lifetime diagnosis of autism spectrum disorder or pervasive developmental disorder (e.g. autism, Asperger syndrome, Rett's syndrome)
4. Current diagnosis of developmental delay or intellectual disability
5. Suicidal ideation with a plan or intent or a suicidal attempt within the past 12 months
6. History of diagnosis of (a) drug and/or alcohol abuse within the past 12 months
7. Current use of benzodiazepines (e.g. lorazepam, clonazepam, alprazolam, diazepam, triazolam) or certain sleep aids (zolpidem, eszopiclone, zaleplon)
8. Previous Woebot application use
9. Enrollment of more than one member of the same household.

3.2 Screen Failures

Participants who sign study assent/consent and do not meet inclusion criteria at Screening, will be considered a Screen Failure. Participants who screen fail will return to the clinical care pathway at CHKD. Re-screens will not be permitted in this study.

3.3 Withdrawal of Participants from the Study

If a participant decides to withdraw consent from the study, they will be removed from all future study activities. In addition, a participant may be withdrawn by the investigator if the participant violates the study plan, or for administrative and/or other safety reasons. Those randomized into the W-GenZD condition will be removed from the study app and program if withdrawn. All data collected prior to withdrawal may be used in descriptive summaries and/or analyses.

3.3.1 Violation of Study Plan

Participants that do not complete registration for the W-GenZD application or who do not attend a teletherapy group within the first week following randomization will not be removed from the study for failure to access the study intervention. Participants will remain in the study and will continue to receive invitations to complete survey assessments. Depending on randomized condition, those in the CBT-Lite group may attend the remaining sessions (2-4) and those in the W-GenZD group may download the app and program the duration of the 4-week intervention period. All participants randomized to this protocol, regardless of participation or withdrawal status, will be included in the intent-to-treat analysis (see section 9.0).

4. Study Design

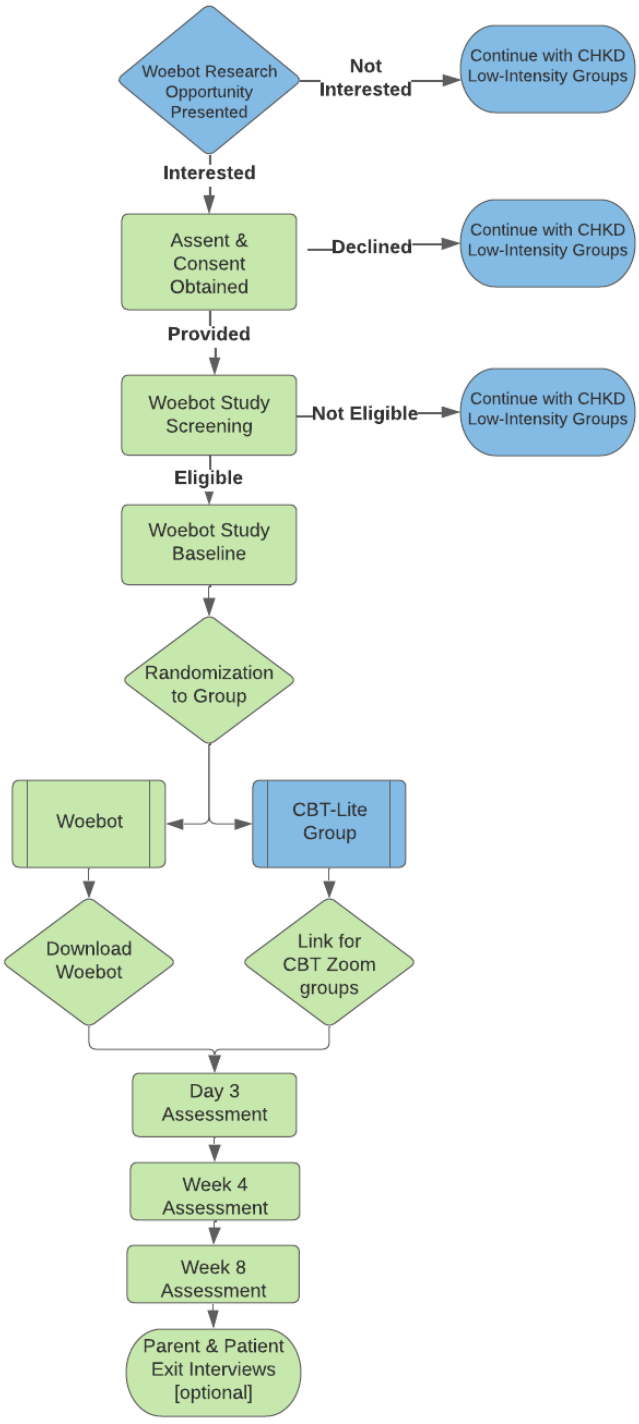
This study will be a randomized controlled trial of W-GenZD versus CBT-lite teletherapy groups. The trial will consist of 3 primary phases: Screening/Baseline, Treatment, and a Follow-up period.

All adolescents referred to the CHKD Mental Health Program are provided an orientation about the clinical care program and participate in a brief clinical triage assessment to assess needed level of care. In general, information about the study and consent to contact is included in the welcome packet. As part of recruitment efforts, CHKD may provide families with tokens of engagement (e.g., stress balls). Based on the brief clinical triage assessment, if the adolescent is appropriate for the low-intensity intervention track, study staff will re-introduce the study during the telephone interview and assess the family's (adolescent and parent/guardian) interest in participating. Research staff will follow up with those who expressed interest, present the study, obtain informed consent and assent, facilitate assessment completion, and assess inclusion/exclusion criteria.

Adolescents who do not meet eligibility criteria will be thanked for their interest and willingness to volunteer, and will return to the routine clinical care pathway at CHKD.

Adolescents who meet inclusion criteria after completing the screening and baseline questionnaires will be randomized 1:1 to the treatment groups. Participants who are randomized will enter the 4-week treatment period where they will engage in the assigned group treatment and complete assessments at study day 5, week 2, and at end of treatment, week 4. At week 4, study application access and participation in the teletherapy groups will end and participants will complete a follow-up assessment at the end of study, week 8.

Figure 1. Participant flow through study



4.1 Treatment Arms

4.1.1 W-GenZD Mobile Application

W-GenZD is a mobile application program that delivers evidence-based therapy for the symptoms of mild-moderate depression and anxiety in adolescents in brief "conversations" with a fully automated relational agent called Woebot. It is a brief, self-guided 4-week intervention that draws from CBT, IPT-A and elements of dialectical behavior therapy (DBT), depending on the presenting situation, to help the adolescent develop emotion regulation skills in the context of their everyday life. In this way, the mobile application is designed to be targeted, relevant, and integrated into the lived experience of adolescents, capable of delivering the appropriate technique for the problem at hand, at the time of need. W-GenZD was adapted from and differs from the broader Woebot platform in key ways.

1. Unique Check-In Flow
2. Unique Onboarding
3. Unique Content Modules
    a. Psychoeducational Lessons: New topics such as Media Literacy and Identity
    b. Psychotherapeutic Tools: New tools for Communication Analysis and Conversation Role-Play, as well as Relationship Development
    c. Behavioral Health Problem Areas: expanded Sleep, Communication, Procrastination, Loneliness, and Anxiety areas.

W-GenZD was built from a synthesis of:

1. Human-centered design process, to understand the needs and lived experience of adolescents with depression,
2. Interviews with clinicians expert in adolescent mental health, which highlighted and underpinned the breadth and nuance in clinical presentation and therapeutic approach, and
3. Critical analysis of the literature on current standard of care, effective approaches, modalities, and problems to be solved.

Participants will gain access to the study application once randomized throughout Week 4 (EOT) and are encouraged to use the app for a minimum of 5 minutes per day during the treatment period.

4.1.2 CBT-Lite Teletherapy Groups

The CBT-Light teletherapy groups aim to provide support to adolescents seeking treatment after they have been triaged into CHKD's low-intensity track. In the clinical setting, CHKD offers CBT-lite teletherapy groups for youth with low intensity symptoms who are waiting for individual care, as described above. The research-specific groups are a brief, 4-week intervention held once weekly for an hour, and limited to those participating in this protocol. Enrolled participants randomized to group are offered the group that best fits their schedule. An assigned study clinician will facilitate each teletherapy group with up to 10 adolescents in each session. Each group begins with orientation and reviewing group rules, individual check-ins with each participant (rating stress level and hopefulness), followed by a guided mindfulness moment.

Groups will be conducted on an open-enrollment, rolling topic basis, allowing for participants to join the next available session following randomization and complete all 4 sessions during their study treatment period. Sessions are designed to draw from elements of CBT and the 4 topics include: Building a coping tool box, Accept your feelings, Challenge negative thoughts, and Problem solving.

Fidelity to group process is monitored by non-clinician study team member.

Participants randomized to the CBT-Lite TeletherapyGroup will be offered access to the Woebot LIFE app at the end of study.

5. Study Assessments and Procedures

All assessments, and their corresponding administration points, are listed in Table 1.

5.1 Demographic Questions

At screening, basic demographic information including gender and sexual identity, racial background, and level of education will be collected.

5.2 Psychiatric History

Participants' parent/guardian will be asked at screening about their child's history of psychiatric illnesses, specifically those exclusionary to this study, and for any prior or concomitant medications and therapy. Information around current and past year suicidality and substance use will also be collected.

5.3 CHKD Brief Clinical Needs Assessment

If a participant is deemed eligible for the low-intensity CHKD track and consents for this research study, the following data from the CHKD triage and brief-clinical needs assessment will be collected at screening to help establish eligibility:

- Preliminary diagnosis (given presenting problem(s) of depressive or anxiety symptoms)
- Low-intensity track eligibility, by rule out of the following:
    - Suicidal ideation within the last 2 weeks or be a current risk to self/others
    - Psychotic presentation
    - Meets criteria for an eating disorder
    - History of mania
    - Substance use disorder (as the primary clinical problem)
    - Imminent risk of expulsion
    - Currently prescribed 4 or more psychotropic medications

Additional triage and brief-clinical needs assessment data will be collected from CHKD, as it becomes available based on completion by the family, and may include the following:

- Triage assessment scores:
    - Ask Suicide Screening Questions (ASQ)
    - Safe Environment for Every Kid (SEEK) Parent Questionnaire
    - Strengths and Difficulties Questionnaire (both parents/guardian and adolescent)
    - Pediatric Quality of Life (PQL) (both parents/guardian and adolescent)

5.4 Clinical Outcomes

The following clinical outcomes will be collected via survey platform by adolescent self-report.

<u>The Patient Health Questionnaire (PHQ-8)</u>
The 8-item PHQ, an abbreviated version of the PHQ-9, the PHQ-8, will be used to assess mood and anxiety symptoms respectively. The PHQ-9 is a widely used self-report measure, with demonstrated reliability and sensitivity to clinical

change. The PHQ-8 excludes an item assessing suicidality [34].

Generalized Anxiety Disorder (GAD-7)
The GAD-7 item scale is a brief self-report tool to assess the frequency and severity of anxious thoughts and behaviors over the past 2 weeks. It is a widely utilized, reliable, and valid measure of anxiety [35].

Mood and Feelings Questionnaire (MFQ)
The MFQ short-version is a child self-report assessment consisting of a series of 13 descriptive phrases related to the participant's recent feelings and behaviors. Respondents reflect on whether the phrases are "true", "sometimes true", or "not true" of the subject's feelings and behaviors during the past two-week period [36].

5.5 Working Alliance

Working Alliance Inventory (WAI-SR)
The WAI-SR is a measure of therapeutic bond and consists of a composite score and three subscales; Bond, Goal, and Task. Bond measures the strength of the therapeutic relationship between the client and therapist. Goal measures agreement on the goal of the overall therapeutic program between the client and therapist. Task measures agreement between the client and therapist, regarding the specific activities needed for a therapeutic change to occur such as doing an exercise to ameliorate a specific symptom [37]. The present study utilized the validated 12-item Short Revised version (WAI-SR) with minor changes to language, replacing "therapist" with the name of the assigned treatment group.

5.6 Acceptability and Feasibility

The Client Satisfaction Questionnaire (CSQ-8)
The CSQ-8 is an 8-item measure used to assess client's satisfaction with treatment on a 4-point scale (1 = "very dissatisfied" to 4 = "very satisfied"). Example questions include, "how would you rate the quality of service you received?" and "did you get the kind of service you wanted?" Total sums range from 8-32, with high scores indicating greater satisfaction with W-GenZD. The CSQ-8 has been widely disseminated and considered both valid and reliable (α ranges = .83-.93) [38].

Satisfaction Questionnaire
Participants will be asked 3 open-ended questions about what they found most helpful about their treatment arm, what would make it better, and if there is any other feedback they would like to share.

Usage Rating Profile Intervention (URPI)
URPI-Feasibility and URPI-Acceptability are both 6-item subscales from the URP-Intervention Revised (URP-IR) scale. Responses range from 1 = "slightly disagree" to 6 = "strongly agree". Scores are averages, with greater scores indicating greater intervention feasibility or acceptability. The URPI-Feasibility inquires about factors that impact treatment usage (i.e., intervention quality) and has acceptable reliability, internal consistency, and discriminant validity. The URPI-Acceptability inquires about intervention acceptability. It has demonstrated high reliability and internal consistency [39].

Safety Procedures
Utilization data, including frequency, type, and outcomes, will be collected throughout this protocol to report on incidents of Safety Net Protocol triggers and the occurrence and relatedness of AE/SAEs.

App Engagement

Data characterizing mobile application use, including days in app and content engagement, will be collected throughout treatment (4-weeks) for participants randomized to the W-GenZD treatment arm.

Group Attendance

Group attendance will be kept by facilitators/study coordinator throughout the study and provided through the EDC from randomization through the end of treatment (4-weeks) for those randomized to the CBT-lite teletherapy treatment arm.

Healthcare Utilization

Data regarding a participant's healthcare resource utilization (HCRU), social determinants of health and comorbidity data will be collected throughout the pre-study, treatment and follow-up periods. Participants will have various lengths of engagement within the CHKD system, therefore pre-study HCRU data will be collected from the time of first engagement through entering the study and until end of study. This will include CPT and ICD codes, diagnoses (e.g., EHR Problem List data), treatments including medications related to pediatric visits in the CHKD system, (emergency department visits, pediatric and mental health care office visits, outpatient behavioral health care visits, and medications available for services provided in the CHKD health system) and any relevant lifetime psychiatric assessments (e.g., Vanderbilt, PHQ).

5.7 Parental Check-Ins

At weeks 2, 4, 6, and 8 a study personnel will conduct a telephonic visit with the participant's parent/guardian. During these calls information regarding AE/SAEs and concomitant medications will be collected. These calls will also serve as an opportunity to address any trouble-shooting around the use of the application or attendance to the CBT-lite teletherapy group. See Appendix 1. for full guidelines for these check-ins.

5.8 Unscheduled Telephone Visit: Safety Response

If at any time following consent, through the end of study, that an adolescent has a safety event, defined as a risk or actual harm to self or others, qualified study personnel will conduct an immediate unscheduled protocol visit (telephone contact). Study personnel will learn of these events through several methods:

1. A participant in the Gen-ZD treatment group confirms a crisis in the mobile app (See Section 6.)
2. A CBT-lite teletherapy group facilitator learns of risk during group session
3. Is contacted directly by a participant or parent/guardian

During the unscheduled telephone visit, the clinician will assess suicidality, thoughts of self-harm or harm to others, including plan and intent, as well as protective measures and a safety plan. For the full SNP Response procedures and guidelines, refer to Appendix 2.

5.9 Participant and Parent/Guardian Exit Interview

The goal of the post-study interviews is to identify opportunities for product improvement. This includes discussion of the participant's mental health journey & typical concerns, as well as their experience with the product. During study consent, participants will be presented with the opportunity to consent to this optional study procedure. Following study completion at 8-weeks, if consent was granted to be contacted for an exit interview, a study representative will reach out and schedule with participants based on availability. Efforts will be made to interview participants equally from both treatment arms of the study. Due to availability of interview appointments and potential number of interested participants, not all who express interest in this optional procedure will be contacted.

6. Safety Net Protocol (SNP)

Woebot's (W-GenZD) natural language processing algorithm was designed to detect language that suggests a user may be in imminent crisis. Specifically, it will detect if a user inputs, via free response text entry, a phrase or word(s) that matches an a-priori determined and thorough list of such phrases and word(s) that may be used in imminent crisis situations. After the algorithm detects these words, it will inquire if it is indeed a crisis situation. If the user says yes, the application will notify the participant that the on-call study clinician will be reaching out to provide support and assess safety.

After notification of the safety response follow-up, W-GenZD will offer to help that person in the moment with their upsetting thoughts. This is clinically relevant because suicidal thoughts are thoughts that can be addressed through cognitive therapy techniques. Our value herein is to support and provide in-vivo skills to someone who seeks assistance in changing their emotions and thoughts in the moment.

Once a crisis has been confirmed, W-GenZD will send a HIPAA compliant alert (via Jabber, Spok, or other mutually agreed upon communications channel) to designated clinical staff who will be on call to provide 24/7 coverage of these alert messages. This individual, who will be on the study team, will be embedded in the CHKD system of care, and therefore in a position to triage the individual, engage directly with the participant to ensure their safety and wellbeing, and/or refer to emergency services as necessary. Triage decisions resulting from the clinical alerts will be separately logged, in HIPAA complaint fashion, for purposes of improving the Safety Net Protocol.

7. Concomitant Medication and Therapy

While many adolescents who are seeking services may not be prescribed psychotropic medications, those that are connected to treatment will be allowed to participate in this study and continue their current regimen if the following inclusion/exclusion criteria is met:

1. If currently prescribed antidepressant medications (e.g. escitalopram/Lexapro, fluoxetine/ Prozac), antipsychotic medications (e.g. aripiprazole, asenapine, olanzapine, paliperidone, quetiapine, risperidone), or stimulants (e.g. amphetamine/Adderall, Methylphenidate/Ritalin) and alpha agonists (e.g. atomoxetine/Strattera, Guanfacine/Intuniv), they are at a regular, stable dose for at least 60 days at screening with no plans to change medication/dose throughout the study
2. Is not currently using benzodiazepines (e.g. lorazepam, clonazepam, alprazolam, diazepam, triazolam) or certain sleep aids (zolpidem, eszopiclone, zaleplon)

Use of concomitant medications throughout the study will be collected at baseline, week 4 EOT and week 8 EOS.

8. Risk and Benefit Assessment

8.1 Risks

Given that the research aims to enroll participants into a low-risk intervention that replaces a passive waitlist, we do not anticipate that participation in the study will be associated with elevated risk. Participation in the study is independent to pharmacological treatments being utilized by participants and we do not anticipate that participation in the study will impact pharmacological treatments. The overall evaluation of risk is that it is low.

8.1.1 Misunderstanding the Capabilities of the Application

W-GenZD is not intended to be a crisis service, however given the nature of the targeted population and experience of depression, there is the potential participants may misunderstand the limitations of the app. To

mitigate this risk, the study will provide clear information on the capabilities of the app, intended use, and limitations of the SOS feature at consent/assent, randomization, and key points throughout. Additionally, when a safety event is triggered, an on-call CHKD clinician will receive an immediate notification and follow-up with the participant as outlined in the Safety Net Protocol.

8.1.2 Data Breach

All study data, from participant self-report and CHKD study personnel, are gathered on either a HIPAA-compliant web platform that resides behind Woebot Health security firewalls or via a HIPAA-compliant survey platform, thus actual risk from data breach for study data is low. Research material obtained from human subjects will involve behavioral and psychological assessments including self-report questionnaires. All data obtained via Woebot will be encrypted and stored on Amazon Web Services (AWS) and/or Google Cloud Platform; Woebot Health data gathering and storage procedures are compliant with both HIPAA and the European Union's General Data Protection Regulation. Only members of the research team will have access to identifiable study data. De-identified data will be accessible to the product development team (designers, user researchers, and product managers) as well as the research team.

8.1.3 Potential Upset due to Study Procedures

Foreseeable risks to participants include the possibility that some assessment questions and/or treatment procedures may be upsetting to participants. Experience with similar populations has indicated that the risk of emotional upset during the assessments is low and if it occurred, the upset would likely be temporary and not be serious in nature. Such risks will be minimized by the thoughtful selection of questionnaires. Participants will also be informed that they may withdraw from the study at any time and if requested, appropriate resources will be provided.

There is also a potential risk of distress at the end of the assigned study intervention(s). Participants are informed during the consent process, and are reminded at randomization, parental check-ins at weeks 2 and 4, and at the end of the surveys at week 4 that they will no longer have access to the study intervention(s) after week 4. Return to care and other resources are provided at week 6 and the end of the study at week 8 or earlier if deemed necessary by clinician assessment.

Participants can refuse and withdraw from participation at any time. If they withdraw consent from the study, they will no longer have access to the study treatments.

8.2 Benefits

When evaluating the risks and benefits of the proposed study, it is believed that risks are relatively minimal when compared to the potential therapeutic benefits that subjects are likely to receive. The possible benefits of receiving Woebot or participating in the CBT-lite teletherapy groups include potentially improving mood (anxiety, stress, and/or depression), acquiring practical psychotherapeutic skills (from cognitive behavioral therapy, dialectical behavior therapy, and mindfulness), and receiving psychoeducation about mental health.

Participants who improve mood may derive additional benefits should said mood improvements be associated with other psychological improvements such as interpersonal or occupational functioning. Study of the effectiveness of the W-GenZD intervention will also benefit society more generally by providing data on the efficacy of Woebot.

9. Statistical Analysis

This study was designed to assess the feasibility of delivering W-GenZD as an option for adolescents ages 13-17 years triaged into a low intensity track for mental healthcare while on a waiting list for definitive treatment.

Primary Aim: What is the feasibility and acceptability of the W-GenZD among a group of adolescents and who have been screened and triaged into low-intensity treatment within CHKD?

Hypothesis: W-GenZD will be acceptable and feasible.

Primary Endpoints: Feasibility and acceptability metrics including:

- Study enrollment rates
- URPI -Feasibility; UPRI - Acceptability {12 items}
- Client Satisfaction Questionnaire (CSQ-8) {8 items}
- App engagement metrics {Woebot condition}
    - *Measure*: App engagement, including number of messages sent to Woebot by week and number of days active in the app by week
    - *Measure:* Content and program satisfaction ratings, including data collected in app (e.g., module ratings)

Analysis Plan:
Statistical analysis will be descriptive. Continuous variables will be summarized using tables of descriptive statistics: number of participants with recorded observations, mean, standard deviation, median, first quartile, third quartile, minimum, maximum and interquartile range (IQR) . Study enrollment rates will be reported. For subjects in the Woebot condition the app engagement measures will be summarized. Similarly, the content and program satisfaction ratings, including data collected in the app will be summarized. Categorical and ordinal variables will be described using frequencies and percentages. . The amount of missing data will be summarized by treatment condition.

Secondary Aim: What is the preliminary comparative efficacy of W-GenZD and CBT-lite telehealth zoom groups to manage mood and anxiety concerns?

Hypothesis: W-GenZD will be non-inferior to CBT-lite with regards to the secondary endpoints at 4-weeks end-of-treatment

Secondary Endpoints:

- PHQ-8

Analysis Plan:
To assess the secondary aim non-inferiority tests will be used. The secondary analysis will focus on meeting the secondary aim of an initial test of the non-inferiority of W-GenZD as compared to CBT-lite telehealth zoom, to manage mood concerns. An intent-to-treat analysis will be used with participants analyzed as assigned to the treatment conditions. Mean, standard deviation, median, first quartile, third quartile, minimum, maximum and interquartile range (IQR) will be reported for each variable at each time point. A non-inferior test will be employed. The margin of clinical significance for the outcomes will be set to 2. These tests will be performed for each variable using the end of treatment time point. In addition, a meta-analysis will be performed to assess the active control effect of the cbt-based telehealth in a pediatric population. Full details will be specified in the SAP.

Tertiary Aim**:** Investigate potential between group differences..

Tertiary Endpoints:

- Working Alliance Inventory-SR (WAI-SR)
- GAD-7
- MFQ

Analysis Plan:
The tertiary analysis will focus on meeting the tertiary aim of an initial test of the potential between group differences on the WAI-SR, GAD-7, and MFQ. An intent-to-treat analysis will be used with participants analyzed as assigned to treatment conditions.

Exploratory Aim**:** To observe and describe upon the utilization and outcomes of the safety procedures utilized within this study (Safety Net Protocol, AE/SAEs and device relatedness). For each AE/SAE type, and Safety Net Protocol, *n* will be reported. To explore healthcare utilization, social determinants of health, and comorbidity data for pre-study and during-study (treatment and follow-up) periods.

Exploratory Endpoints:

- Safety Net Protocol, AE/SAEs and device relatedness
- Pre-period and study-period healthcare utilization data. This will include:
    - Diagnosis (e.g., ICD code) and service rendered (e.g., CPT code)
    - Emergency Department utilization
    - Primary care utilization (e.g., primary care well visit and sick visit appointment)
    - Behavioral-health related utilization (psychiatry, psychology, other therapist, etc)
    - Psychiatric medication prescriptions
    - Social determinants of health information (e.g., food and housing insecurity and social work utilization)
    - Comorbidity data (i.e., any additional behavioral health or physical health diagnoses)
    - Problem List
    - Any relevant lifetime psychiatric assessments (e.g, Vanderbilt, PHQ)

Analysis Plan: Primary care utilization, behavioral health care visits utilization, psychiatric medication utilization, Emergency Department visits utilization, social determinants of health, comorbidity and diagnoses data, and psychiatric screenings where relevant will be summarized using descriptive statistics for W-GenZD and CBT-lite telehealth zoom groups.

9.1 Interim Report

Readout of complete baseline sample descriptive statistics (demographics, enrollment data, etc) and baseline scores of measures will be completed after the last patent randomizes into the study.

10. Adverse Event Reporting and Follow-Up

10.1 Definitions

Adverse Event (AE): Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study device, whether or not considered related to the product.

Serious Adverse Event (SAE): Any adverse event requiring medical treatment or other major interventions.

10.2 Assessment

Due to the low-risk profile of this study, adverse and serious adverse events are not anticipated. The investigator will be alert to any complaints or adverse reactions that arise and will take appropriate steps to alleviate the difficulties as soon as possible.

10.2.1 Time Frame

Any event observed or reported from the time of randomization through the final study visit (week 8) will be collected.

10.2.2 Causality Rating

An event's relatedness to the investigational device will be determined by the Principal Investigator and classified under the following causality ratings:

Non-related: There is no evidence of any causal relationship.

Related**:** There is clear evidence of a casual relationship between the device and event; all other explanations have been ruled out.

10.2.3 Severity of ADE

Mild: Awareness of sign, symptom , or event , but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity and may warrant intervention.

Severe: Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

10.3 Reporting

The designated study team will report an event to the Sponsor within 24 hours of learning of it. The investigator should make every attempt to obtain as much information as possible and must assess the relationship of the event to the study device and complete the AE/SAE assessment form. It is understood that more may be learned about the event after the initial report and this information may and should be updated as collected.

Any event that the sponsor determines is/are reportable to the IRB will be made within 5 working days of when the sponsor makes that determination. If it should be determined that an event presents an unreasonable risk to all participants, the study or parts of the study presenting that risk will be terminated as soon as possible.

11. Study Key Personnel

CHKD Principal Investigator: Mary Margaret Gleason, M.D., FAAP

Dr. Gleason is a pediatrician and child and adolescent psychiatrist. She is Division Director of Child and Adolescent Psychiatry at Eastern Virginia Medical School and Vice Chief of Mental Health at Children's Hospital of the King's Daughters (CHKD). As Principal Investigator of the proposed study, Dr. Gleason will organize overall research activities and is responsible for execution of the protocol as outlined in the Contractual Agreement between the Sponsor (Woebot Health) and the Institution (CHKD).

Woebot LIaison: Emil Chiauzzi, PhD.

Emil Chiauzzi, Ph.D. is Woebot's Director of Research and a clinical psychologist with extensive digital health research experience. As Co-Investigator of this protocol, he will participate in protocol planning, study monitoring, and reviewing data from the study. If the study proceeds to manuscript preparation for journal submission, he will participate as a coauthor.

Woebot Liaison: Athena Robinson, Ph.D.

Athena Robinson, Ph.D. is Woebot Health's Chief Clinical Officer and a clinical psychologist with extensive experience in clinical outcomes research and intervention leadership utilizing evidence-supported theory and

treatment. She has served as Principal Investigator and Co-Investigator on numerous trials. Dr. Robinson will play an integral role in this project's development and will maintain involvement and oversight as the project enrolls participants.

CHKD Co-Investigator: Nicole Wells, Ph.D.

Dr. Wells is a licensed psychologist with a specialization in child psychology. She is an active clinician and has experience in research. Dr. Wells will participate in planning of the research study and support day to day implementation of the project.

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Appendix 1. Parental Check-In Guidance

At protocol Visits 3, 4, 5, and 6 (Weeks 2, 4, 6, and 8), study personnel will conduct a telephone visit with the participant's parent/guardian.

1. Conduct an AE/SAE assessment
2. Inquire if there have been any changes to the participant's medical/psychiatric history or concomitant medication/therapy
3. Address any technological trouble-shooting they may be experiencing (W-GenZD application use or accessing the CBT-lite teletherapy groups)
4. Remind the parent/guardian of next visit and expectations in the study

On average, telephone visits should last between 5-15 minutes depending on the parent/guardian report.

Data from these calls will be captured in the EDC under the appropriate week's telephone visit form.

Appendix 2. Unscheduled Telephone Visit: Safety Response Follow-Up

If a safety risk is identified during a group CBT-lite teletherapy session:

1. Request that the at-risk participant stay on after group or arrange an immediate direct call if necessary
2. Administer the ASQ and fully evaluate the participant's self-harm or suicidal ideation/plan/intent, or harm to others
3. If the participant is not at imminent risk, review protective measures and a safety plan
    a. If an imminent risk is identified, contact the parent/guardian and/or emergency services
4. Contact the participant's parent/guardian or identified emergency contact to provide an overview of the risk and discuss the safety plan
5. Submit the Unscheduled Visit: Safety Response data collection form

If you receive a notification that a participant has confirmed a crisis in the mobile app:

1. Make immediate attempts to contact the participant's parent/guardian or identified emergency contact
    a. 3 attempts within 1 hour should be made
        i. Recommended method is first by text message, followed by direct phone calls
2. If contact is made, share the reason for the call, inquire about the participant's whereabouts and if they are available to speak with the clinician
    a. If participant is available, administer the ASQ and fully evaluate the participant's self-harm or suicidal ideation/plan/intent, or harm to others
    b. Review protective measures and a safety plan with the participant and then with the parent/guardian
3. If contact **can not** be made with the parent/guardian or identified emergency contact, contact emergency services
4. Submit the Unscheduled Visit: Safety Response data collection form

If a parent/guardian, identified emergency contact or participant contacts you directly with a safety concern:

1. If participant is available, administer the ASQ and fully evaluate the participant's self-harm or suicidal ideation/plan/intent, or harm to others
    a. If not an imminent risk, review protective measures and a safety plan with the participant
    b. If an imminent risk is identified, contact the parent/guardian and/or emergency services
2. Follow-up with the parent/guardian or identified emergency contact if they did not initiate contact in order to provide an overview of the risk and discuss the safety plan
3. Submit the Unscheduled Visit: Safety Response data collection form

Following any identification of an Adverse or Serious Adverse Event (AE/SAE) or a contact to Emergency Services under the above guidelines, study clinicians should continue to follow-up with the family appropriately until the event has been determined to be resolved. Proper AE/SAE reporting timeframes should be followed.