A Multicenter, Randomized, Double-Blind, Controlled Study Evaluating the Efficacy and Safety of a Digital Therapeutic WB001 as an Adjunct to Treatment as Usual Among Women with Mild to Moderate Postpartum Depression

NCT05551195

November 3, 2022

Protocol Number: **WB001-001**

NCT Number: **[TBA]**

Date; Version **03-Nov-2022**

Clinical Trial Protocol WB001-001

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Document Type: Clinical Trial Protocol
Clinical Trial Phase: Pivotal
Version Number: 1.6

CLINICAL STUDY PROTOCOL	
Title:	**A Multicenter, Randomized, Double-Blind, Controlled Study Evaluating the Efficacy and Safety of a Digital Therapeutic WB001 as an Adjunct to Treatment as Usual Among Women with Mild to Moderate Postpartum Depression**
Protocol Number:	**WB001-001**
Test Product:	**WB001 (Class II Software Medical Device)**
Regulatory Agency Identifier Number(s):	**[TBA]**
Sponsor:	[redacted]
Contract Research Organization:	[redacted]
Coordinating Investigator:	**[TBD]**
Protocol Version and Date:	**v.1.6 03-Nov-2022**

This study will be performed in compliance with the principles of Good Clinical Practice.

AMENDMENTS FROM PREVIOUS VERSIONS

Date	Version	Brief Summary of Changes
16-May-2022	**1.0**	Original version
03-Jun-2022	**1.1**	SCR/BL changed from Day 0 to Day 1
05-Jul-2022	**1.2**	Update to Study Title; Removal of CAGE-AID assessment and clarification of planned SCID-5-CT modules; Clarification of engagement data monitoring; Exclusion #11 updated to "Previous Woebot use" from "Previously participated in a Woebot study"; Added section 5.4 for the collection of Healthcare Utilization information
15-Jul-2022	1.3	Revised Section 9.1 (Model 3) per the Statistical Analysis Plan; Protocol Title updated throughout for consistency
09-Aug-2022	1.4	Addition of the 'Program Assignment Assessment' (Section 5.5); Updated the description of the Secondary Objective/Endpoint, Interim Analysis, and Blinding Analysis to be consistent with the current SAP; Updated Figure 3; Update "Resources" to "Helplines" to align directly to Product feature (pg 32, pg 49)
14-Oct-2022	1.5	Updated Benefit/Risk Assessment; Addition of minimum necessary operating system requirements to Section 4.4; Updated screenshots in Appendix 2
03-Nov-2022	1.6	Sponsor address updated; Update to levels of clinical concern being reported to DSMB and reporting timeframe (10 to 5 day) in Section 7

PROTOCOL SIGNATURE PAGE – SPONSOR AND CRO

This protocol has been reviewed and approved by the representative(s) listed below. Any modification of the protocol must be agreed upon by the Sponsor and the investigator and must be documented in writing.

Woebot Health representative(s):

Print Name	**Title**
Signature	**Date**

IQVIA representatives:

Print Name	**Title**
Signature	**Date**

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by Woebot Health, and given approval/favorable opinion by the institutional review board, and I agree that it contains all necessary details for my staff and I to conduct this study as described. I will provide copies of the protocol and any amendments to all study personnel under my supervision and provide access to all information provided by Woebot Health or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from Woebot Health. It is, however, permissible to provide information to a participant in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, participant to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice, and applicable regional regulatory requirements.

I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by Woebot Health and inspection by the appropriate regulatory authorities.

I agree to make my participants' study records available to Woebot Health personnel, their representatives, and relevant regulatory authorities in order to verify data that I have entered the case report forms. I will retain the study-related essential documents until Woebot Health indicates that they are no longer needed. I am aware of my responsibilities as an investigator as provided by Woebot Health.

I understand that Woebot Health may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Woebot Health.

Investigator Name (Print)	**Title**
Institution:	
Signature:	**Date**

PROTOCOL SYNOPSIS

Protocol Number: WB001-001
Full Title: A Multicenter, Randomized, Double-Blind, Controlled Study Evaluating the Efficacy and Safety of a Digital Therapeutic WB001 as an Adjunct to Treatment as Usual Among Women with Mild to Moderate Postpartum Depression
Abbreviated Title: [Study Evaluating the Efficacy and Safety of WB001 as an Adjunct to TAU in Postpartum Depression]
Sponsor: Woebot Health
Coordinating Investigator: [TBA]
Study Type: Interventional
Planned Number of Subjects: 210, with interim analysis for sample size re-estimation
Study Sites: Up to 25 study centers within the U.S.
Primary Objectives: The purpose of the study is to determine whether, for women diagnosed with PPD, WB001 with adjunctive Treatment as Usual (TAU; WB001+TAU) can reduce symptoms of depression compared to an educational control with adjunctive TAU (Ed Control "ED001" +TAU), at the end of treatment (EOT; 8 weeks) as measured by the HAM-D6. **Primary Aim: To evaluate the efficacy of [WB001+TAU] vs. [ED001+TAU] on depressive symptoms at EOT as measured by a structured clinical interview with the 6-item Hamilton Rating Scale for Depression (HAM-D6; Ruhe et al 2005) among women diagnosed with postpartum depression (PPD).**
Secondary and Other Objectives: **Secondary Aims:** ● **To evaluate the effectiveness of [WB001+TAU] vs. [ED001+TAU] at EOT on indices of clinical interest (1) mother infant bonding (with the Mother-Infant Bonding Scale (MIBS)); (2) Edinburgh Postnatal Depression Scale (EPDS), (3) Patient Health Questionnaire (PHQ-9); and (4) Generalized Anxiety Disorder Questionnaire (GAD-7).** ● **To evaluate the within-group differences on the HAM-D in the [WB001+TAU] and [ED001+TAU] arms between BL and EOT.**

Exploratory Aim: Investigate clinically significant between group differences of [WB001+TAU] vs. [ED001+TAU] on the Clinical Global Impression (CGI) Scales and the Patient Global Impression (PGI) Scales.
Study Design: This protocol comprises a randomized, double-blind, controlled trial to assess the efficacy and safety of 8 weeks of treatment with either [WB001+TAU] or [ED001+TAU] in a population of women with mild to moderate PPD. Patients will be referred by an obstetrician, pediatrician, or other healthcare professional, or by other digital and site based recruitment methods and if interested, will complete the pre-screening process. Those confirmed as eligible will be scheduled to attend a screening/baseline onsite visit, at which they will complete an informed consent form and the Principal Investigator (PI), or qualified site staff and Central Independent Rater (CIR) will conduct screening assessments. The PI or sub-investigator will determine participant eligibility. Eligible participants will be randomized to one of the two groups and will receive instructions on downloading and using the smartphone application (app) to which they were randomized. Participants will use the app as instructed and will attend telehealth visits with the CIR who will administer an assessment for the primary endpoint (e.g., HAM-D6) and PI/qualified site staff who will administer key assessments for the safety endpoints at Weeks 4 and 8 by video call (preferred) or telephone. Participants will also complete several questionnaires (electronic patient-reported outcomes [ePROs]) on their own. All assessments will be completed within 3 days prior to or 3 days (±3) after participants' Week 4 and Week 8 key assessment visit date.
Study Duration: 8 weeks
Target Population: Women with mild to moderate PPD who are ≤ 92 days postpartum
Key Inclusion Criteria: ● **Must have primary residence in the United States** ● **Must be willing to comply with all study procedures and restrictions** ● **Must be able to understand and willing to provide informed consent** ● **Must be ≤ 92 days postpartum at the time of screening** ● **Must be women aged 22-45 years who had onset of a major depressive episode any time during pregnancy or within 4 weeks following delivery according to DSM-5 diagnostic criteria (Segre et al., 2013)** [redacted] ● **Must own or have regular access to a smartphone (Android or iOS smartphone with a recent, supported operating system), and has reliable Wi-Fi access or sufficient data plan to engage with assigned treatment condition for the duration of the study**

- **Must have current mild-moderate depression as measured by the HAM-D6 score > 7 and < 13 (i.e., between 8-12, inclusive) at screening (Bech et al., 2007; Pridmore et al., 2020)**
- **Participant must confirm having a form of TAU, defined as clinician supervised outpatient care management and includes follow-up visits, medication, psychotherapy, or some combination thereof**
- **As part of TAU during the study, any confirmed concomitant medications and/or psychotherapy are permissible and must be regularly scheduled or stable (dose and frequency) for over 4 weeks prior to baseline (BL) visit**

Key Exclusion Criteria:

- **Gestation less than 28 weeks**
- **HAM-D6 score ≤ 7 or ≥ 13 (severe depression) at Screening**
- **Currently pregnant or plans to become pregnant within the next 8 weeks**
- **History of drug and/or alcohol use disorder within the past 12 months measured by the SCID-5-CT (Williams JB, 2015)**
- **Lifetime history of suicide attempt or ideation with a plan and intent to harm oneself during the current episode of PPD** [redacted]
- **Current or lifetime psychosis, including history of post- and peri-partum psychosis as measured by the SCID-5-CT (Williams JB, 2015)**
- **Current or lifetime history of schizophrenia, schizoaffective disorder, bipolar disorder, and/or homicidal or infanticidal ideation as measured by the SCID-5-CT (Williams JB, 2015)**
- **History of antidepressant treatment with ketamine/esketamine, electroconvulsive therapy, vagal nerve stimulation, or a deep brain stimulation device**
- [redacted]
- **Fetal demise within the past 18 months**
- **Previous Woebot use**

Study Conditions: 1:1 randomization to either [WB001+TAU] or [ED001+TAU]

[redacted]

Control Device: The educational control application is an educational app named ED001. [redacted]

Treatment as Usual (TAU): Participants will receive TAU, which is clinician supervised outpatient care including follow-up visit(s), psychotropic medication, psychotherapy, or some combination thereof.

Primary Endpoint: Difference in HAM-D6 scores between groups at EOT, controlling for baseline (BL) and other covariates

Secondary Endpoints:

1. **Difference between arms in the following assessments at EOT, controlling for BL and other covariates:**
    - **Edinburgh Postnatal Depression Scale (EPDS)**
    - **Maternal-Infant Bonding Scale (MIBS)**
    - **Patient Health Questionnaire-9 (PHQ-9)**
    - **Generalized Anxiety Disorder-7 (GAD-7)**

2. **Difference in HAM-D6 scores within arms between BL and EOT**

Exploratory Endpoints:

- **Change from baseline in Clinical Global Impression-Improvement (CGI-I) the CGI-Severity (CGI-S) at Week 4 and Week 8**
- **Change from baseline in Patient Global Impression-Change (PGI-C) and Patient Global Impression-Severity (PGI-S) at Week 4 and Week 8**
- **Client Satisfaction Questionnaire-8 at Week 8**

Safety Endpoints: C-SSRS and Adverse Events (AEs), Serious Adverse Events (SAEs)

Safety Aim: To evaluate the safety of [WB001+TAU] versus [ED001+TAU] based on PI and Sponsor determined AE and SAEs. The study will use the Columbia-Suicide Severity Rating Scale (C-SSRS), the PHQ-9 item #9, and the EPDS item #10, and the HAM-D17 item #3 to facilitate identification of AEs and SAEs. It would be separately determined whether identified AEs or SAEs are related to the device.

Statistical Methods: The primary efficacy endpoint is the difference between treatment arms in the HAM-D6 score at Visit Week 8 after controlling for baseline and other covariates. For the ITT population, a restricted maximum likelihood (REML) based linear MMRM approach will be used to test for systematic differences in change between arms over time, after accounting for participant-specific heterogeneity in HAM-D6 scores residual error structure. The MMRM will be parameterized to include random effects for site and repeated measures for post-baseline visits using an unstructured residual covariance structure (3 parameters); in the unlikely event that the unstructured covariance matrix fails to converge, the model will be refit with a first order autoregressive covariance matrix (2 parameters).

This test will be performed using the final, MMRM model-based t-test with a two-sided significance level of 5%. Estimated least squares means for change from baseline and the observed absolute values (± SE) at each visit by treatment group will be plotted over time. **No explicit imputation will be performed; the MMRM model described above will be run on this population, which implicitly imputes missing data under a missing at random (MAR) assumption.** **As a sensitivity analysis for the primary analysis using ITT population, MMRM model in the same manner as described above will be conducted in the PP population.** **The treatment effectiveness on MIBS, EPDS, PHQ-9, and GAD-7 (difference between arms at Week 8, controlling for baseline) will be evaluated using the same analysis plan proposed for the analysis of the primary endpoint (HAM-D6).** **Subgroup analyses will be accounted for by including potential subgroups as covariates in the primary analysis model.**
Protocol Version and Date: [v1.6] [11.03.2022]
[redacted]

CONTENTS

1. INTRODUCTION

1.1 Background

Childbirth is perhaps the most significant event and transition a woman may undergo in her lifetime. The period following childbirth organically brings significant lifestyle, occupational, relational, and physical health changes that may result in exhaustion, pain, anxiety, frustration, and guilt, as well as happiness and excitement.

Postpartum depression (PPD) is the occurrence of a major depressive episode with onset during pregnancy or within the first four weeks following childbirth (American Psychiatric Association, 2013). In contrast to a major depressive episode outside of the peripartum phase, in PPD, the pervasive negative thoughts are mainly related to the infant and surrounding sequela. For example, extreme worry about the infant may present at clinically significant levels (Norhayati et al., 2015) and intrusive thoughts about inadvertent and accidental potential harm to the infant are ubiquitous (Pearlstein et al., 2009).

In the United States, as many as 1 in 5, up to 20%, of peripartum women experience PPD, although the actual prevalence may be much higher because of limited screening and/or underreporting (Centers for Disease Control and Prevention, 2020; Davey et al., 2011).

PPD presents an early risk to the infant, the mother-infant bond, and to the family unit as a whole (Hamdan & Tamim, 2011). Specifically, PPD is associated with adverse maternal, infant, and child outcomes, such as lower rates of breastfeeding initiation and shorter duration (Wouk et al., 2017), reduced or poor maternal-infant bonding (Stein et al., 1991), and infant developmental disorders (Kingston et al., 2012).

Reducing maternal depression has been correlated with positive outcomes for both mother and child, including mediating improvements in childhood behavioral problems among 3- to 4-year-old children (Shaw et al., 2009).

1.2 Study Rationale

Published recommendations from the American College of Obstetricians and Gynecologists (ACOG; The American College of Obstetricians and Gynecologists, 2018), the United States Preventive Services Task Force (USPSTF) (O'Connor et al., 2016; United States Preventative Services Taskforce, 2016), the American Psychiatric Association (APA), and the National Institute for Health and Care Excellence (NICE) (National Institute for Health and Care Excellence, 2020; Pilling et al., 2009) recommend early screening and treatment for PPD, and some specifically recommend follow-up visits with the maternal care provider. Using the Pregnancy Risk Assessment Monitoring System (PRAMS), CDC research shows that nationally, about 1 in 5 (20%) women experience symptoms of postpartum depression (CDC, 2020; Bauman et al., 2018). Depressive symptoms in PPD can last more than 6 months among 25–50% of those affected (Anokye et al., 2018). Among all postpartum women, approximately 50% have increased anxiety and depression symptoms (Whitton et al., 1996), yet only 20% report these symptoms to their doctors (Palladino et al., 2011). Almost 60% of peri- and postpartum women with depressive symptoms do not receive a clinical diagnosis and among those who are diagnosed, an estimated 50% receive no treatment (Ko et al., 2012).

APA, USPSTF, and NICE recommend evidence-based psychotherapy, specifically cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), and more recently, computerized CBT (cCBT) without medication as first-line treatment for patients with PPD (National Institute for Health and Care Excellence, 2020; Gelenberg et

al., 2010; Yonkers et al., 2009). Psychotherapeutic interventions are also attractive to providers and patients because they do not involve the risk of exposure to medications that would be present in breast milk (Fitelson et al., 2010). If psychotherapy and counseling are unavailable or unacceptable to the patient, or if depressive symptoms become more severe, a trial of an antidepressant can be considered (Sriraman et al., 2015). These recommendations apply to women with mild to moderate PPD, regardless to if they are breastfeeding. In terms of specific evidence-based psychotherapeutic approaches, psychological interventions founded in CBT and IPT have demonstrated substantive evidence and are recommended for PPD specifically (Stamou et al., 2018).

- CBT

CBT is a manualized psychotherapeutic intervention validated for the treatment of depression based on decades' worth of rigorous research and has been recommended as a primary line of treatment for depression (David et al., 2018) including PPD (Huang et al., 2018; Mu et al., 2021. The CBT model postulates a direct and reciprocal interaction between thoughts, feelings, and behaviors that both helps illuminate understanding of one's overall emotional distress and situational responses as well as simultaneously highlight areas for intervention. Specifically, CBT intervenes on cognitions, primarily through challenging and changing automatic thinking patterns, and behaviors, primarily through behavioral activation (Beck et al., 2011). CBT is a psychosocial intervention that aims to help the patient challenge their thinking and change maladaptive patterns of behavior, and it has proven effective, across multiple systematic reviews and meta-analyses, in treating certain psychiatric disorders such as major depression disorder and anxiety disorders (Barlow et al., 2017; Driessen & Hollon, 2010; Gilson et al., 2009; Knaus, et al., 2014).

- IPT

IPT has demonstrated efficacy for and is a recommended intervention for depression as well as PPD (Grigoriadis, et al., 2007). IPT for depression is based in attachment and interpersonal theory and postulates that the depressive symptomatology has biopsychosocial roots and are therefore in part, consequences of interpersonal distress in one of four IPT defined problem areas including: role disputes, role transitions, grief, and interpersonal deficits. IPT for PPD mirrors this theoretical foundation and primarily focuses on role disputes, role transitions, and grief and loss. IPT targets interpersonal functioning towards the reduction of clinical symptomatology (Weissman et al., 2008), and it is an efficacious and recommended intervention for depression (Pilling et al., 2009) as well as PPD (Stuart et al., 2012).

Woebot Health (hereafter noted as the Sponsor) developed WB001 as a digital therapy intended to deliver CBT and some elements of IPT, to women who have recently given birth, to reduce the symptoms associated with PPD. As a mobile patient application WB001 is a treatment modality that may fill an unmet need for patients with PPD to access psychotherapeutic tools, under clinical supervision and as an adjunct to treatment-as-usual (TAU) which includes follow-up visits, psychotherapy, or medication (or some combination thereof).

This study is being conducted to evaluate and compare the efficacy of [WB001+TAU] and an educational control (ED001) [ED001+TAU] on reducing symptoms of PPD as measured by the 6-item Hamilton Rating Scale for Depression (HAM-D6) among women diagnosed with mild to moderate PPD.

1.3 Investigational Device

WB001 is a smartphone application designed for an 8-week treatment period, as an adjunct to TAU for women aged 22-45 years with mild to moderate postpartum depression. Specifically, women must have given birth in the previous 92 days and have no active or recent history with substance(s) abuse, not be currently psychotic, have no lifetime occurrence of psychosis, schizophrenia or bipolar disorder, or a history of suicide attempt or suicidal ideation or a plan or intent to harm oneself during the current episode of postpartum depression, or history of homicidal or infanticidal ideation via self-report. WB001 is intended as a prescription-only adjunctive treatment under the supervision of a clinician.

WB001 was developed based on evidence for mobile mental health applications, and factors associated with positive outcomes in the literature proposed by Bakker and colleagues (2016), including the following:

- Built on a CBT framework
- Incorporates automated tailoring
- Provides mental health information
- [redacted]
- Addresses both anxiety and depressed mood
- Simple and intuitive interface and interactions
- Real-time patient engagement and check-in reminders

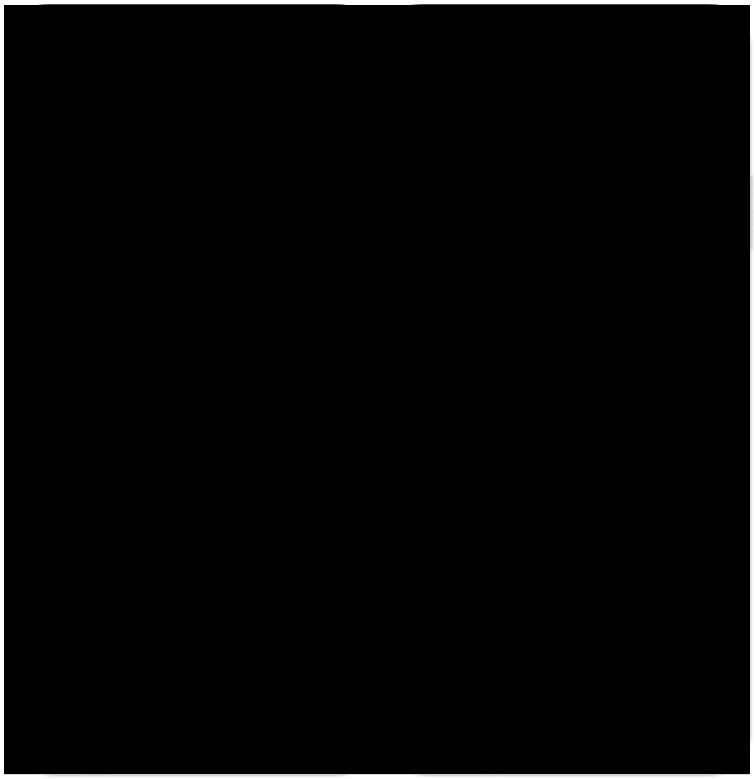
1.4 The WB001 Platform

[redacted]

A. Deep understanding of the lived experience of women with PPD

This device was developed through a multi-phased design process to imbue a deep understanding of the lived experience of women with PPD as well as an understanding of the day to day lives of women who have recently given birth. Women, as well as clinicians, including psychologists, psychiatrists, and obstetricians, who specialize in the treatment of women with PPD were interviewed about their experience to understand the

breadth and nuance of clinical presentation.



[redacted]

Therapeutic working alliance is a construct long recognized as meaningful and predictive of outcomes in psychotherapeutic research (Ardito et al., 2011). The Sponsor has completed a series of studies to understand if Woebot establishes a working alliance, as measured by the Working Alliance Inventory short form (WAI-SR), a widely accepted and psychometrically valid assessment tool (Darcy et al., 2021). Published results from a cross-sectional, retrospective analysis with more than 36,000 Woebot users indicated a working alliance with Woebot was established within 5 days of initial app use and that the level of alliance was sustained through 8 weeks of application use (https://formative.jmir.org/2021). Moreover, the level of working alliance endorsed was analogous to those from recent literature on traditionally delivered outpatient CBT. [redacted] results from an RCT of adult women (*n* =192; 46% White) who had recently given birth indicated that women randomized to the WB001 established a working alliance with Woebot (Ramachandran et al., 2020).

C. Optimizes Treatment Exposure through a Truly Scalable Technology

Despite the evidence base of efficacious therapies for PPD, there are several individual and systemic barriers to treatment access that are specific to this population and underserved populations. These barriers include lack of time, childcare issues, stigma, and fear of loss of parental rights, plus the lack of available psychotherapy and a desire to avoid pharmacological interventions (Manso-Córdoba et al., 2020). [redacted]

[redacted]

Benefit/Risk Assessment

Potential benefits of participating in this study include improved mood, improved mother-infant bonding and wellbeing of the infant, the acquisition of practical psychotherapeutic skills and increased knowledge of mental health. Improved mood could lead to other benefits such as improved interpersonal functioning, ability to return to work (if applicable), and improved performance at work.

[redacted] Overall, there is also a low risk associated with participation in the study due to the study's due diligence to screen and exclude patients with severe depression and other psychosis history or substance abuse. The primary potential risk to the participant that could lead to AEs is the worsening of negative symptoms of PPD. These and other potential risks may be considered minimal, and no greater than those associated with depression behavioral therapies for the treatment of PPD. The participants may experience some AEs due to their underlying condition and/or with the use of adjunctive treatment. The risk profile of standard of care used in clinical practice is well understood and is detailed in their respective package inserts.

However, potential risks include the opportunity cost of seeking alternative treatment, device software failure, leading to delayed access, information security breaches, and potentially brief emotional stress that may result from attending key assessment visits, completing survey questions that cover sensitive topics, and discontinued access to the assigned study intervention at the end of study (Week 8).

Several aspects of the study design will mitigate these potential risks of participating in the study:

- [redacted] adjunct.
- The eligibility criteria will exclude patients with severe psychiatric diagnoses (e.g., psychosis, history of attempted suicide or current suicidal ideation, substance use disorder).
- Concomitant medications and psychotherapy are allowed during the study period per standard of care as prescribed and administered by trained professionals, as long as the medication doses and frequency of psychotherapy are stable for at least 4 weeks before the Baseline visit. The study will capture any changes (e.g., starting or stopping a medication or any change in medication dose or frequency, as well as changes in frequency of psychotherapy).
- [redacted]

- Survey Questionnaires have been thoughtfully selected to minimize the risk of emotional upset due to the topics covered.
- Woebot performing appropriate software verification and validation testing to demonstrate that the device's behavioral therapy has been correctly implemented so that the participant can access it when needed.
- All study data will be gathered on a secure Health Insurance Portability and Accountability Act (HIPAA)-compliant web platform and will be encrypted to minimize the risk of a data breach.
- Participants will be informed that they may leave the study at any time and can receive appropriate referrals for alternative treatment.
- Participants will have contact with the investigator and/or designated clinical rater at each study assessment time point, who will administer validated psychometric assessments to monitor for worsening symptoms and/or the development of suicidal ideation.
- Study withdrawal criteria are designed so that participants who experience worsening of symptoms can withdraw from the study to receive additional treatment, per PI recommendation.
- A Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) will be established with clear rules around study stopping criteria and appropriate assessment of participant safety.

Considering the measures taken to minimize the risks to participants participating in this study, the potential risks identified in association with WB001 are justified by the anticipated benefits that may be afforded to participants with PPD.

2. STUDY OBJECTIVES AND ENDPOINTS

The study objective is to determine if WB001 used adjunctively with TAU can further reduce symptoms of depression for women with mild to moderate PPD beyond that of an educational control application and TAU, at the end of the 8-week treatment period as measured by the change in HAM-D6. The endpoints to support the study objectives are listed in Table 1**.**

TABLE 1 STUDY OBJECTIVES, HYPOTHESES, AND ENDPOINTS

Objective	Endpoint
Primary Objective: **To evaluate the efficacy of [WB001+TAU] vs [ED001+TAU] on depressive symptoms as measured by a structured clinical interview (with the Hamilton Depression Rating Scale (HAM-D) among women diagnosed with PPD.**	**Difference in HAM-D6 scores between arms at end of treatment (EOT) controlling for baseline (BL) and other covariates**
Secondary Objectives:	
• **To evaluate the efficacy of [WB001+TAU] vs [ED001+TAU] on indices of clinical interest including (1) the Mother-Infant Bonding Scale (MIBS), (2) Edinburgh Postnatal Depression Scale (EPDS), (3) Patient Health Questionnaire (PHQ), and (4) Generalized Anxiety Disorder (GAD)**	• **Difference between arms in indices (MIBS; EPDS; PHQ; GAD) at EOT controlling for BL and other covariates**
• **To evaluate the within-group differences on the HAM-D in the [WB001+TAU] and [ED001+TAU] arms**	• **Difference in HAM-D6 scores from BL to EOT within each trial arm**
Exploratory Objective: **Investigate clinically significant between group differences of [WB001+TAU] vs [ED001+TAU] on the Clinical Global Impression (CGI) scales and Patient Global Impression (PGI) scales**	**Difference between arms on Clinical Global Impression of Improvement and Severity (Clinical Global Impression Improvement (CGI-I) the CGI-Severity (CGI-S)) and Patient Global Impression Scales (Patient Global Impression Change (PGI-C) and Patient Global Impression Severity (PGI-S)).**
[redacted]	[redacted]

AE=adverse event; BL=baseline assessment; Clinical Global Impression - Improvement and Severity (CGI-I; CGI-S). EOT=end of treatment assessment; EPDS= Edinburgh Postnatal Depression Scale; GAD=Generalized Anxiety Disorder Questionnaire; MIBS=Mother-to-Infant Bonding Scale; Patient Global Impression – Change and Severity (PGI-C; PGI-S); PHQ = Patient Health Questionnaire; SAE=serious adverse event

3. STUDY DESIGN

3.1 Overall Study Design

This is a multicenter, double-blind, randomized, controlled trial to evaluate the efficacy and safety of WB001 in adult women with mild to moderate PPD. Eligible participants must have diagnosis of mild to moderate PPD and experience at least mild to moderate symptom severity as evidenced by a score of > 7 and < 13 (i.e., between 8-12, inclusive) on the HAM-D6.

The study will utilize referrals by an obstetrician, pediatrician, or other healthcare professional, or by other digital and site based recruitment methods and direct participants to the closest study site, across up to 25 study centers in the U.S., to schedule and complete a pre-screening/screening appointment. From there, the site staff will schedule their first office visit, during which the site staff with oversight by the investigator, will obtain informed consent and complete the screening and BL assessments. The CIR will be responsible for administration of the HAM-D for the primary endpoint as outlined in Appendix 3: Schedule of Events. To standardize and facilitate administration of the primary endpoint, the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) will be used (Williams, J.B. 2015).

Participants will then be randomized in a 1:1 manner to either [WB001+TAU] or [ED001+TAU] and will be prompted to install the app on their smartphone. Study site personnel will help the participants with the app installation to streamline enrollment. Participants in both groups will participate in a form of TAU, which is clinician supervised outpatient care including, follow-up visit(s), psychotropic medication, psychotherapy, or some combination thereof. [redacted] Both treatment arms will be presented as possibly helping to improve PPD and both will be described as the study app so that there is no distinction made to the participants about WB001 or the digital educational control app. Post-randomization, the 8-week treatment period begins when the participant successfully downloads the study app and completes the integrated onboarding process.

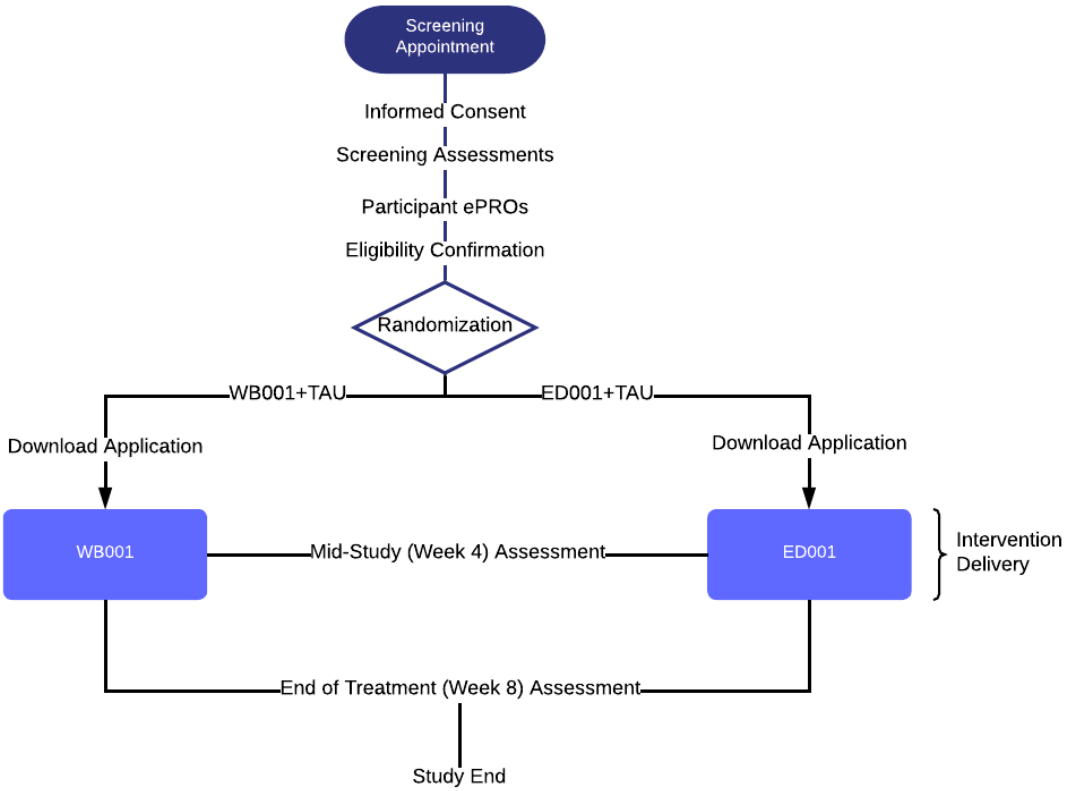
[redacted]

Participants will attend a mid-study and EOT (at Week 4 and Week 8) telehealth visit with a CIR, to be assessed based on the HAM-D, a validated standard clinician-rated and participant-rated outcome scales for PPD. Any AE/SAE raised during CIR-administration of HAM-D, will be raised to the PI or qualified designee for final determination on appropriate course of action. At Week 4 and Week 8 the PI or qualified site staff will

administer the C-SSRS, evaluate for concomitant medications/therapy, pregnancy status, and safety throughout the duration of the trial.

At Week 4 and 8, participants will be prompted to complete several online self-report assessments (e.g., EPDS, PHQ-9, MIBS, GAD-7 and PGI) within 3-days prior to or 3-days after the visit date. The same assessment steps in Week 4 will apply to Week 8 (EOT) visits, with the addition that at Week 8 participants will receive instructions about how to uninstall the app and will go through other end-of-study procedures. [redacted] Not including the referral period and potential for participants to complete the last self-reported assessments 3 days after the week 8 visit, the duration of study participation is 8 weeks. Figure 3 shows the overall Study Schematic.

Figure 3. Study Schematic



3.2 Rationale for Duration of Treatment

As discussed, CBT and IPT have robust efficacy for the treatment of depression in adults including PPD. Although there is no exact standard length of treatment (cognitive behavioral therapy, 2011), flagship models of CBT and IPT were delivered over the course of 12-20 sessions. However, briefer interventions, including guided self-help adaptations of the therapies, have demonstrated meta-analytic level efficacy and durability of effect for depression, including those which are six or fewer weekly sessions (Cuijpers, et al., 2019). Typically, CBT guided self-help delivery ranges from 6 to 8 sessions total (Barth, et al., 2013). A 2021 meta-analysis of online CBT guided self-help interventions found no significant differences on depression outcomes between groups that were short (≤ 4 weeks), moderate (= 4-8 weeks), and greater (≥ 8 weeks) in length (Ma et al., 2021).

[redacted]

[redacted]

3.4 Scientific Rationale for Study Design

To prevent bias in treatment allocation and assessment of treatment effect, the study is randomized.

The chosen efficacy objectives and endpoints represent standard assessments used in clinical studies of treatments for depression and reflect clinically meaningful outcomes for patients with PPD and the clinicians who treat them.

[redacted] The safety data will also add to the Sponsor's understanding of AEs that might be associated with WB001.

The study is designed with telehealth visits, which are more convenient for study participants , and accommodate the need to comply with recommended social distancing recommendations for reducing transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

A participant is considered to have completed the study if she has completed at least BL and Week 4 or Week 8 for primary HAM-D6. The end of the study is defined as the date of the last visit or last procedure of the last participant in the study.

3.5 Blinding

This is a double-blind study. Participants will not be made aware to which intervention they are assigned and will be randomized to receive the active treatment app (WB001) or the Educational Control (ED001). Thus, participants, clinicians, and the clinical site study team will be blinded to treatment allocation to the extent possible throughout the study period and database lock.

[redacted]

[redacted]

[redacted]

TABLE 2 BLINDING PLAN

Role	Event			
	Randomization / Treatment Allocation	Week 4, 8 Assessments	Interim Analysis	Final Analysis
Participants	B	B	B	B
PI and Site staff to administer assessments	B	B	B	B
One Site Coordinator to assist with app registration/download	UB	UB	UB	UB
Site/Central Independent Rater	B	B	B	B
DSMB Statistician will generate the randomization schedule and run analysis queries requested by DSMB members	UB	UB	UB	UB
Independent (non DSMB) statistician and	B	B	B	B

programmer/data analysts for Interim Analysis and Final Analysis (prespecified in SAP)				
B = Blinded; UB = Unblinded				

3.6 Procedure for Breaking the Blind

In the event that a CIR, PI, or blinded site staff member is inadvertently unblinded, the site will be provided with SOPs detailing the appropriate procedure for each of the following scenarios:

1. Unblind a participant and or other study staff in an emergency situation
2. Unblind data for the purpose of notification to the Data Safety Monitoring Board (DSMB)
3. Manage and mitigate accidental unblinding

In the case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Accidental unblinding, which may occur during discussions between the participant and trial PI and site staff, would not impact the primary endpoint which will be collected by CIRs. Any potential unblinding at the CIR level may trigger replacement of the rater. All instances of unblinding will be recorded and assessed for comparability between the groups.

4. STUDY POPULATION

Eligible participants who are enrolled in the trial will be assigned a unique participant randomization number for study app functionality assignment at baseline. Only participants who meet all the inclusion criteria and none of the exclusion criteria will be eligible to participate in the study. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1 Inclusion Criteria

A participant will be eligible for entry into the study if all the following inclusion criteria are met:

1. Participants must have primary residence in the United States
2. Participant must be willing to comply with all study procedures and restrictions
3. Participants must be able to understand and be willing to provide informed consent
4. Participants must be ≤ 92 days postpartum at the time of screening
5. Participants must be women aged 22-45 years who had onset of a major depressive episode during pregnancy or within 4 weeks following delivery according to DSM-5 diagnostic criteria (Segre et al., 2013)

[redacted]

7. Participants must own or have regular access to a smartphone (Android or iOS smartphone with a recent, supported operating system), and has reliable Wi-Fi access or sufficient data plan to engage with assigned treatment condition for the duration of the study
8. Participants must have current mild-moderate depression as measured by the HAM-D6 score > 7 and < 13 at Screening (Bech et al., 2007; Pridmore et al., 2020)
9. Participants must confirm having a form of TAU, defined as clinician supervised outpatient care management and includes follow-up visits, medication, psychotherapy, or some combination thereof.
10. As part of TAU during the study, any confirmed concomitant medications and psychotherapy are permissible and must be regularly scheduled or stable (i.e., dose and frequency, respectively) for over 4 weeks prior to BL visit

4.2 Exclusion Criteria:

A participant will not be eligible for study entry if any of the following exclusion criteria are met:

1. Gestation less than 28 weeks
2. HAM-D6 score, ≤ 7 or ≥13 (severe depression) at Screening
3. Currently pregnant or plans to become pregnant within the next 8 weeks
4. History of drug and/or alcohol use disorder within the past 12 months as measured by the SCID-5-CT
5. Lifetime history of suicide attempt or ideation with a plan and intent to harm oneself during the current episode of PPD [redacted]
6. Current or lifetime psychosis, including history of post- or peri-partum psychosis as measured by the SCID-5-CT (Williams JB, 2015)
7. Current or lifetime history of schizophrenia, schizoaffective disorder, bipolar disorder, and/or homicidal or infanticidal ideation as measured by the SCID-5-CT
8. History of antidepressant treatment with ketamine/esketamine, electroconvulsive therapy, vagal nerve stimulation, or a deep brain stimulation device

[redacted]

10. Fetal demise within the past 18 months
11. Previous Woebot use

4.3 Rationale for ≤3 Months Postpartum

While timing of PPD indicates that the onset of a major depressive episode can occur anytime during pregnancy or within the first 4 weeks after giving birth, the protocol has specified that a woman is potentially eligible to participate in the proposed trial up to 3 months after giving birth. This 3-month period allows time for a woman to be screened for depression at their initial postpartum physical examination with their Obstetrician-Gynecologists, as recommended by ACOG and is the rational for stipulating ≤ 92 as an inclusion criterion for this study. Specifically, this initial in-person, postpartum physical exam, which is recommended standard of care practice, occurs soon after birth or within a few months after birth, depending on method of delivery. ACOG and other professional guidelines recommend screening for PPD at these postpartum visits (O'Connor et al., 2016; United States Preventative Services Taskforce, 2016). The 3-month period for the study allows women to be screened for depression or present for treatment while still maintaining alignment with the clinical definition for onset of PPD.

4.4 Minimum Technology Requirements

Participants should have routine access to their smartphones for the duration of the trial. In order to support the study application, participants' smartphones must meet the minimum necessary operating system requirements (Apple iOS 13 and Android OS 8). In addition, they should be able to attend in-clinic and remote telemedicine visits during the trial as outlined in Appendix 3: Schedule of Events.

4.5 Screen Failures

Participants who consent to participate in the clinical study but fail screening are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of participants who fail screening, to meet the Consolidated Standards of Reporting Trials publishing requirements (Bhatt, 2022), and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any AE/SAEs. Re-screens for medication or psychotherapy stability may only be permitted with investigator approval, given all other inclusion/exclusion criteria are still met.

De-identified participant ID numbers assigned to participants who screen fail will not be reused.

4.6 Study Discontinuation or Withdrawal

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator. The investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being. Involvement in the study is strictly voluntary. Participants have the right to withdraw from the study at any time for any reason, without any reprisal.

Participants should be discontinued from the study if any of the following occur:

1. The participant withdraws consent to participate in the study
2. The participant develops an illness that would interfere with her continued participation in the study
3. The participant has an SAE rated as Grade 3 (severe) or higher (see Table 3 Clinical Concerns Categorizations)

4. The participant is noncompliant with treatment schedule, study procedures, in the opinion of the investigator and per the protocol, where applicable
5. The participant is confirmed to be pregnant (by self-report during scheduled assessment with the investigator/qualified site staff at Week 4 and 8)
6. The PI, Sponsor, IRB, or regulatory agency requests withdrawal of the participant
7. Any other reason relating to the participant's safety or integrity of the study data as determined by the DSMB

Participants who withdraw from the study may be replaced. Participants who withdraw or are withdrawn from the study cannot subsequently rejoin the study.

If a participant withdraws or is withdrawn from the study, the study Sponsor, sites, and DSMB will be informed immediately. If there is a medical reason for withdrawal, the participant will remain under the supervision of the investigator until satisfactory health has returned or appropriate referrals have been made and executed upon.

Unless a participant withdraws consent for follow-up procedures, they should continue to attend all scheduled study telehealth visits, including the EOT visit. Even if a participant declines to participate in the remaining scheduled telehealth visits, she will be encouraged to attend an early withdrawal visit, with the same assessments as the Week 8 EOS visit, as indicated in Appendix 3: SoE.

If the participant withdraws consent for disclosure of further information, the Sponsor may retain and continue to use any collected data before such a withdrawal of consent.

Although a participant is not obliged to give a reason for withdrawing from a study, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant's rights.

4.7 Lost to Follow-up

A participant will be considered lost to follow-up and withdrawn from the study if they fail to attend both scheduled key assessments visits (Week 4 and Week 8) and are unresponsive to multiple reminders and communication from the study site. Participants that miss one key assessment visit (Week 4 OR Week 8) will be permitted to continue in the study.

The following actions must be taken if a participant fails to attend a required telehealth study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or site staff designee must make every effort to regain contact with the participant, where possible. Sites will be instructed to complete at least 3 separate outreach attempts to participant via phone, text, or email (with 1 being a direct telephone call). These contact attempts should be documented in the participant’s electronic case report form (eCRF) and in the EDC system.

5. DESCRIPTION OF STUDY ASSESSMENTS

Study assessments and procedures, including their timing over the 8 weeks of treatment are outlined in the SoE (see Appendix 3) and described in the subsequent subsections. Participants will be instructed to adhere to the study design schedule and to complete all required assessments and procedures. The CIR-administered HAM-D will be administered by clinical psychologists who have been appropriately trained. The Protocol Supplement (separate document) provides more detail on the specific study assessments, including response options, scoring etc.

5.1 General Screening/Baseline Assessments

After obtaining informed consent from the participant, the PI or site staff will assess the participant for eligibility as outlined in the inclusion/exclusion criteria and administer screening/baseline assessments (see Appendix 3). Some assessments are for screening purposes only, e.g., the Structured Clinical Interview for DSM-5 - Clinical Trials Version (SCID-5-CT).

The SCID-5-CT (First, et al., 2016) is a structured diagnostic interview for diagnosing the major psychiatric disorders found in DSM-5 that is tailored and streamlined to the primary inclusion criteria of the study. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. The interview participants may be either psychiatric or general medical patients—or individuals who do not identify themselves as patients, such as participants in a community survey of mental illness or family members of psychiatric patients. The SCID-5-CT is used in the research context to assess common disorders in mental health and will be customized for this study to specifically assess the diagnoses of major depressive disorder (MDD), current and lifetime diagnosis of a psychotic disorder including postpartum psychosis and Schizophrenia. Participants will also be assessed for bipolar disorder, homicidal or infanticidal ideation, and history of drug and/or alcohol use disorder within the past 12 months, in accordance with the inclusion criteria.

Demographics

Demographic data, including year of birth/age, sex, ethnicity, and race, will be recorded.

Previous and Concomitant Medications and Therapy

Previous and concomitant medications and therapy will be recorded by self-report at the time of screening/baseline visit and reconciled by study personnel. Any changes in medication and/or therapy would be confirmed through the study period. For this study, concomitant medications are those being taken at the time of screening or during the study.

At a minimum, concomitant medications will include all Rx drugs, standing or pro re nata (PRN) medication for dose, route, and frequency. The study will allow for exceptions of collecting common over the counter (OTCs) (e.g., ibuprofen, acetaminophen) and prescription medications (e.g., antibiotics) for minor transient ailments (i.e., non-sedating antihistamines to treat seasonal allergies or a cold). The following details must be recorded:

- Medication name (generic name)
- Reason for use
- Start and end date of administration
- The dose and frequency of administration
- Participation in psychotherapy
- The frequency of psychotherapy sessions
- Primary reason for psychotherapy

The PI should be contacted if there are any questions regarding concomitant medication.

Any changes in concomitant medications meaning a change in dose or frequency of a medication or the introduction of a new intervention or discontinuation of existing intervention will be recorded by site staff, whether the medications are for PPD, MDD, or other conditions.

Medical History

Medical history, including previous and ongoing illnesses (including psychiatric), will be recorded by site staff, with the start date and end date (if applicable) of the illness or condition. Any pre-study procedures will be recorded in the eCRF as part of the medical history assessment. Any AEs that begin between the time of informed consent and the first use of the blinded study intervention will be recorded as an AE/SAE and unrelated to the device.

Pregnancy History And Pregnancy Status

Obstetrical medical history, including total number of previous pregnancies, will be recorded by site staff in the eCRF, with applicable dates.

Although pregnancy is exclusionary and a participant who becomes pregnant during the study will be withdrawn, there are no protocol-specific requirements for pregnancy testing or contraceptive use. Changes in pregnancy status will be completed via self-report during key assessment visits. There are no precautions regarding breastfeeding during the study because the intervention is not a medicinal product.

5.2 Efficacy Assessments

The following table summarizes the efficacy and safety assessments that will be used for primary, secondary, and exploratory endpoints during the study period.

Assessment	Endpoint Type	Definition
HAM-D	**Primary**	• **The HAM-D17 is a 17-item clinician-rated measure of depression (Hamilton, 1960).** • **The HAM-D6 is a subset of the HAM-D17 that assesses 6 core items associated with major depression: depressed mood (item 1), feeling of guilt (item 2), difficulty performing work and activities (item 7), motor retardation (item 8), psychic anxiety (item 10), and somatic symptoms (general, i.e., low energy and bodily pain) (item 13)** • **Item 13 is scored 0 to 2 (0 = none/absent to 2 = most severe) and all other items are scored 0 to 4 (0 = none/absent to 4 = most severe).** • **Total score ranges from 0 to 22 and a higher score indicates greater severity of depression.** • **The HAM-D is commonly used for diagnostic purposes in research, and structured clinical interviews such as this are recommended to formally diagnose clinical depression (Norhayati et al., 2015).** • **The HAM-D17 will be administered at baseline via the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D 17-item HAM-D), at Week 4, and Week 8 to derive HAM-D6**
EPDS	**Secondary**	• **A brief self-report questionnaire used as a screening tool to identify patients who are at risk for perinatal depression (Cox et al., 1987; Wisner et al., 1994).** • **The 10-item scale assesses depression criteria (including anhedonia, anxiety, sleep disturbance, and suicidal ideation) in the past seven days.** • **Each item has four ordinal response options, yielding a total score of 0 to 30 where a higher score denotes greater depression (values ≥ 10 denote possible depression).** • **The EPDS is a widely used measure with demonstrated reliability and validity for the assessment of depression (Yawn et al., 2009; Zhong et al., 2014), and is also routinely used in clinical care practice for the assessment of patients with PPD.** • **The EPDS will be administered at baseline, Week 4, and Week 8.**

PHQ-9	**Secondary**	• **A 9-item, self-report questionnaire that evaluates frequency and severity of depression symptoms within the previous 2 weeks.** • **The 9 items are based on the DSM-4 criteria for major depressive disorders (American Psychiatric Association, 2000).** • **Each item is scored on a 4-point Likert scale from 0 (not at all) to 3 (nearly every day).** • **It is a widely used self-report measure; it has demonstrated reliability and sensitivity to clinical change.** • **Scores of 5, 10, 15, and 20 represent cut points for mild, moderate, moderately severe, and severe depression, respectively (Kroenke & Spitzer, 2002).** • **The PHQ-9 will be administered at baseline, Week 4, and Week 8.**
GAD-7	**Secondary**	• **This is a 7-item, self-report questionnaire for assessing how often respondents have been bothered by anxiety symptoms over the last two weeks (Spitzer et al., 2006).** • **Each item has 4 ordinal response categories: Not at all (0); Several days (1); More than half the days (2); Nearly every day (3). Responses are summed to yield a score from 0-21, where higher scores denote greater anxiety** • **Scores of 5, 10, and 15, represent cut points for mild, moderate, and severe anxiety, respectively (Spitzer et al., 2006).** • **It has demonstrated reliability, validity, and responsiveness (Dear et al., 2011).** • **The GAD-7 will be administered at baseline, Week 4, and Week 8.**
MIBS	**Secondary**	• **A self-report questionnaire consisting of 8 words such as "loving," "joyful," or "disappointed."** • **Mother's rate each of the 8 words using a 4-point Likert scale (very much, a lot, a little, or not at all) to indicate how they feel about their baby in the first few weeks.** • **Five of the words describe negative emotional responses and are reverse scored (Taylor et al., 2005).** • **Total scores can range from 0 to 24, with lower scores indicating good bonding.** • **The MIBS will be administered at baseline, Week 4, and Week 8.**

CGI-S	**Exploratory**	• **A single item, 7-point Likert scale to measure the overall severity of the patient's current clinical presentation and symptomatology. (Busner et al., 2007)** • **The investigator will rate the participant's severity of illness based on clinical interviews and assessments relative to their experience with other patients with the same diagnosis.** • **Response choices include 0 (not assessed) and range from 1 (Normal, not at all ill) to 7 (Among the most extremely ill patients).** • **The CGI-S will be administered at baseline, Week 4, and Week 8.**
CGI-I	**Exploratory**	• **A single item, 7-point Likert scale to measure the overall improvement in the patient's condition at the end of treatment. (Busner et al., 2007)** • **The investigator will rate whether the participant's total improvement was due entirely to the intervention.** • **Response choices include 0 (not assessed) and range from 1 (very much improved) to 7 (very much worse).** • **The CGI-I will be administered at Week 4 and Week 8.**
PGI	**Exploratory**	• **The Patient Global Impression scale (PGI), also known as Subject Global Impression (SGI), is the PRO counterpart to the Clinical Global Impressions scale, (CGI), which was published in 1976 by the National Institute of Mental Health (US). (Snyder et al., 2020)** • **Consists of one item based on the CGI and is adapted to the patient.** • **The PGI mainly measures change in clinical status (PGI-C) but can also measure disease severity (PGI-S) or disease improvement (PGI-I).** • **PGI-S is administered at baseline, Week 4, and Week 8; PGI-C is only administered at Week 4 and Week 8.**
Client Satisfaction Questionnaire	**Other/ Exploratory**	• **Participants will be prompted to complete an 8-question Client Satisfaction Questionnaire (CSQ) to assess their level of satisfaction with WB001 vs. ED001 applications.** • **The CSQ will be administered at Week 8.**

5.3 Safety Assessments

To further manage risk in this clinical trial of WB001, the study will incorporate validated psychometric assessments conducted at regular intervals to monitor for worsening symptoms and/or the development of suicidal ideation. The study population will only include participants with mild-moderate depression (inclusion

criterion) and specifically excludes patients with severe depression and prior history of treatment-resistant depression (exclusion criteria). The study will also appropriately monitor worsening of symptoms through the following:

a. Administering the C-SSRS at BL, Week 4, and Week 8

b. Administering the PHQ-9 (item #9), EPDS (item #10), and HAM-D (item #3) at BL, Week 4, and Week 8

c. This protocol continues to adhere to FDA guidance that appropriate assessments, such as assessing for AE/SAEs and administering the C-SSRS, should occur at each planned visit wherein the other clinical assessment will be administered. Thus, the assessment schedule for the C-SSRS mirrors that of the HAM-D.

d. Study participants are welcome to initiate contact anytime throughout the duration of the study with their site. If the contact is attributable to safety reasons, then an Unplanned Visit would ensue, wherein qualified study personnel would follow-up with the participant in a timely manner, and if needed administer the C-SSRS.

Scenarios that would trigger an escalation for an Unplanned Visit include:

- [redacted]

Adverse Events

At each telehealth visit, the PI and site staff will evaluate participants for any changes that could indicate AEs. Participants with AEs will be followed, recorded in the EDC and reported in line with the procedures described in Section 7. Participants will be instructed to contact the study site if any new symptoms occur in between the weeks of telehealth visits. The CIR is responsible for detecting, documenting, and recording any potential safety events based on the administered HAM-D (i.e., score of ≥ 2 on HAM-D17 item #3) that may meet the definition of an AE or SAE, but the investigator will remain responsible for following up on all safety events to confirm if an AE/SAE has occurred and determine the appropriate course of action. The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 7.

Suicidal Ideation and Behavior Risk Monitoring

The study design includes assessment of suicidal ideation as described. All participants will meet with the investigator or qualified site staff at Baseline, Week 4, and Week 8 during a telehealth visit, and will be administered psychometric tests (i.e., C-SSRS and HAM-D item #3) to assess suicidal ideation.

C-SSRS

The clinician-administered C-SSRS is a measure used to identity and assess individuals at risk for suicide (The Columbia Lighthouse Project/Center for Suicide Risk Assessment, 2019). The C-SSRS measures four constructs: the severity of ideation, the intensity of ideation, behavior, and lethality. The C-SSRS is made up of ten categories, with binary responses (Yes or No) to indicate presence or absence of the behavior, and the outcome is a numerical score obtained from these categories. The C-SSRS will be administered by the investigator or qualified site staff during telehealth visits at baseline, Week 4, and Week 8 to monitor for potential onset of suicidal ideation. If a score on the C-SSRS raises a safety concern, i.e., 'yes' on questions 4 or 5, or answer 'yes' to "actual attempt" question in "Suicidal Behavior" section the site-based rater will immediately contact the PI/sub-investigator to ensure that the investigator urgently conducts an assessment of this participant to determine the appropriate actions to take and disposition of the participant. Similarly, if a safety concern is raised due to a score submitted through a CIR administered structured clinical interview (a score of ≥2 on the HAM-D17 item #3) or self-report ePROs (a score of ≥2 on item #9 of PHQ-9 and/or score of >2 on item #10 of EPDS), an electronic system at the sites will notify the investigator to review each incident and follow up with the participant within 24 hours to determine if any action is required. If so, the investigator will be responsible for administering a formal assessment using the C-SSRS, if deemed necessary.

[redacted]

[redacted]

Pregnancy and Breastfeeding

Although pregnancy is exclusionary and a participant who becomes pregnant during the study will be withdrawn, there are no protocol-specific requirements for pregnancy testing or contraceptive use. Changes in pregnancy status will be completed via self-report during key assessment visits. There are no precautions regarding breastfeeding during the study because the intervention is not a medicinal product.

Details of all pregnancies in female participants will be collected after the start of study intervention and until end of Week 8.

If a pregnancy is reported, the site staff and/or investigator will record pregnancy information in the EDC and submit it to the Sponsor within 24 hours of learning of the female participant's pregnancy and initiate withdrawal from the study.

12-lead Electrocardiogram, Vital Signs, and Physical Examinations

These assessments are not scheduled as part of the study; however, if deemed necessary, the investigator may arrange for participants to be referred for medical evaluation.

Unscheduled Visits

Study participants are welcome to initiate contact anytime throughout the duration of the study with their site. If the contact is attributable to safety reasons, then an Unscheduled Visit would ensue, wherein the qualified study personnel would follow-up with the participant, and if needed administer the C-SSRS.

5.4 Healthcare Utilization

Healthcare service utilization will be assessed via participant reports. At Day 1 and at each subsequent assessment, participants will be asked to indicate the number of all-cause and (separately) mental health-related encounters or visits they had for themselves in the previous month/4 weeks within the following categories of service: inpatient (hospital), emergency department, and outpatient medical; outpatient psychotherapy and psychotropic prescription utilization will also be assessed. Additionally, participants will be asked at each assessment (Weeks 4 and 8) to report the healthcare service utilization (i.e., inpatient/hospital, emergency department, and outpatient services) of their new babies during the previous month/4 weeks.

5.5 Blinding Assessment

The success of maintaining the participant blind will be evaluated by the 'Program Assignment Assessment'. This two question patient reported scale will be administered at Week 8 and ask participants to select the treatment group which they believe they were assigned to (see additional details in the SAP).

6. STUDY STOPPING RULES

Study procedures will be stopped if the Sponsor in discussion with the DSMB, IRB, and/or investigator(s), as applicable, determines that the number and/or severity of AEs or abnormal safety monitoring tests justify putting the study on hold. See Section 7.4 Data Safety Monitoring Board (DSMB).

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

The study may resume following the safety review, if the PI and Sponsor agree it is safe to proceed.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

6.1 Early Study Termination

The study can be terminated by the Sponsor at any time. Reasons for early termination include:

- Study recruitment or retention is too low for the study to provide meaningful results
- Unanticipated, significant, or unacceptable safety risk to participants enrolled in the study

- Decision based on recommendations from PI and DSMB after review of safety and efficacy data
- Discontinuation of study if PIs, in collaboration with study clinicians and DSMB, determine from planned analyses that the app is not efficacious or if there are safety concerns.

In taking the decision to terminate, the Sponsor and DSMB will always consider the participants' welfare and safety. Should early termination be necessary, participants must be seen as soon as possible to conduct a formal assessment and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or Sponsor depending on the local regulation will be responsible for informing Institutional Review Boards (IRB) of the early termination of the trial.

7. DATA AND SAFETY MONITORING

Data monitoring will be conducted by the research coordinator and site staff (research team) and overseen by project PIs.

During data collection and monitoring, study coordinators will follow an internal safety protocol and alert a study PI of any clinical concerns. A clinical concern is defined here as any negative experience or symptom that occurs during baseline or post randomization sessions that are raised via email/text/phone correspondence directly by the patient, or in key assessment visits to the CIR, whether it is associated with participation in the study.

The PIs in consultation with study site staff will be responsible for monitoring participant safety during the study and will review relevant data/information to determine 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.

Given this study will be conducted among women with PPD, there are clinical concerns that may be anticipated in the target patient population due to the natural course of disease. Anticipated clinical concerns may include suicidal ideation, clinically significant deterioration in depressive symptoms, self-injurious behavior, suicide attempts, and completed suicide. These events will be recorded and will be elevated to AE or SAE status if deemed appropriate by the investigator, and promptly reported to the Sponsor. As part of a Safety Monitoring process, all AEs/SAEs will require DSMB review, and the Sponsor can query any PI-determined AEs/SAEs.

Table 3 Clinical Concerns Categorizations

Clinical Concern	Definition
0 - Not a clinical concern:	**Qualified research personnel determined that triggering event was not a clinical concern**

1- Mild clinical concern:	**Qualified research personnel determined that triggering event doesn't require investigator input and will continue to monitor participant's responses**
2- Moderate clinical concern:	**Qualified research personnel determined that triggering event requires investigator input. PI/Clinician determined that the research team should continue to monitor participant's responses but that no follow-up was needed.**
3- Elevated clinical concern:	**Qualified research personnel determined that triggering event requires clinician input. PI/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 provider.**
4- Significant clinical concern:	**Qualified research personnel determined that triggering event requires clinician input. PI/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 clinical concerns documented as level 4 of concern will be reported to the DSMB for review and oversight within 5 working days to ensure patient safety and efficient monitoring. In addition, appropriate reporting will be done to notify the Sponsor and IRB per details in Section 10.2 Institutional Review Board.

7.1 Adverse Events

An AE is any unanticipated medical occurrence in a participant or clinical study participant using an investigational product that does not necessarily have a causal relationship with this product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

All AEs recorded during the study period will be assessed for: severity grade (mild, moderate, severe, fatal/life-threatening, relationship to the study treatment or conduct, duration, and whether it is deemed an SAE as defined by Sponsor and requires an action taken regarding study treatment to avoid a negative outcome(s).

7.2 Assessment of Adverse Events

AE Severity

Investigators will grade the severity of all AEs using the Common Terminology Criteria for Adverse Events (CTCAE). If possible, investigators should report event terms that reflect a single, unifying diagnosis rather than individual signs or symptoms (e.g., "influenza" instead of "coughing, body aches, fever;" and "anemia" rather than "low hemoglobin").

If an AE term is not listed in the CTCAE criteria, a corresponding grading is to be performed by the investigator based on his/her best medical judgment as follows:

- **Mild (Grade 1):** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- **Moderate (Grade 2):** minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL)
- **Severe (Grade 3):** medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care ADL
- **Life-threatening (Grade 4):** life-threatening consequences; urgent intervention indicated
- **Fatal (Grade 5):** death related to an AE

AE Causality

Investigators are required to systematically assess the causal relationship between the AEs and SAEs and the treatment using the following definitions:

An event should be reported as related to the study treatment if it follows a reasonable temporal sequence to use of the investigational device and cannot be reasonably explained by the participant's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications); OR the AE follows a reasonable temporal sequence to use of the investigational device and is a known reaction to the investigational device.

An event should be reported as unrelated to study treatment if it does not follow a reasonable sequence from an investigational device, or it can be reasonably explained by the participant's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

7.3 Serious Adverse Events

An SAE is any AE that meets any of the following criteria:

- Results in death
- Is *life-threatening*
- Requires inpatient *hospitalization* or prolongation of existing hospitalization
- Results in persistent or significant *disability/incapacity*
- Is an *important medical event*

Unanticipated Adverse Device Effects

A suspected unanticipated adverse device effect (UADE) is defined as an untoward and unintended response to a study treatment, which is not listed in the applicable product information, and meets at least one AE or SAE criterion, and is assessed as causally related to the study treatment. The Sponsor or designee will be responsible for carrying out required reporting to investigators, health authorities, and other entities as required by law.

Documenting and Reporting Adverse Events and Serious Adverse Events

Reporting of non-serious AEs and SAEs will begin at the time of first interaction with the app and will continue through EOT. Any new clinical condition or worsening of existing conditions between the time the informed consent form (ICF) is signed, and the first use of the study intervention will be recorded as AE/SAEs unrelated to the device.

AEs and SAEs may be reported spontaneously by participants, discovered as a result of general, non-leading verbal questioning by the study staff, or determined by assessments. As needed, qualified study staff will inform investigators to inquire about any new symptoms or worsening of symptoms during the telehealth visits at Weeks 4 and 8. In the interim, participants will be instructed to contact the investigator if new or worsening symptoms develop outside of key assessment visits. All incidences confirmed as AEs or SAEs will be monitored and recorded in the eCRF throughout the entire study.

The investigator must pursue and obtain adequate information about all incidences they deem as AEs and SAEs. At minimum this includes a description of the event, severity, device relatedness, start and stop times, duration, outcome, and any action (e.g., treatment/follow-up tests). The investigator must also assess whether the event meets the criteria for classification as an SAE.

It is the investigator's responsibility to review all documentation (e.g., hospital notes, laboratory reports, and diagnostic reports) related to an AE or SAE. Whenever possible, a single unifying diagnosis should be reported as the event term, and not the individual signs and symptoms.

Investigators are not obligated to actively seek AEs or SAEs after the participant's conclusion of study participation. However, if the investigator learns of any SAE, including death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the investigational device or study participation, the investigator must promptly notify the Sponsor.

Reporting of Serious Adverse Events

The investigator must immediately report SAEs to the Sponsor or designee (no later than 24 hours after becoming aware of the event) using the SAE report form.

The investigator is obliged to promptly respond to any request for follow-up information (e.g., additional information, event outcome, final evaluation, or other records if needed) and to any question from the Sponsor or designee. This timely reporting is necessary to ensure prompt assessment of the event by the Sponsor or designee and to allow them to meet strict regulatory timelines associated with expedited reporting obligations for SAEs.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

All serious and/or possibly related or related (to the device or study procedure) AEs will be reported to the DSMB and reviewed on an on-going basis throughout the participant enrollment and follow-up period as specified in the DSMB charter to ensure the safety of participants enrolled in this study. The DSMB may request additional information as needed. Based on safety data, the DSMB may recommend that the Sponsor modify or discontinue the study; however, all final decisions regarding study modifications rest with the Sponsor.

AE and SAE Follow-up

During the study (and after the EOT visit), all AEs and SAEs should be followed proactively by the investigator or qualified designee until the event resolves, or the condition stabilizes to a level acceptable to the investigator, until the event is otherwise explained, or until the participant is lost to follow-up. New or updated information will be recorded in the originally completed eCRF and the investigator will submit any updated SAE information to the sponsor within 24 hours of receipt of the information.

Safety Reporting Oversight

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor or designee will inform investigators of findings that could adversely affect participant safety, impact the conduct of the trial, or alter the IRB's approval/favorable opinion to continue the trial.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an investigational treatment. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators.

An investigator who receives an investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure (IB) and will notify the IRB, if appropriate, according to local requirements.

7.4 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board is co-responsible for the oversight and safety monitoring of the study. The DSMB advises the Sponsor regarding the continuing safety of the trial participants and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The team assembled for the DSMB will have relevant and complementary expertise in psychiatry, obstetrics and gynecology, clinical trial design, digital health, and statistics. This DSMB should include members from academic sites independent of the study sites and should consist of at least one non-study, board-certified psychiatrist and one biostatistician.

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. Developing the DSMB Charter that will be approved by the Sponsor (including study stopping criteria and final interim analyses being conducted by the independent statistician etc.)
2. 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
3. Recommending alterations to the study design
4. Approving the study protocol before commencement
5. Performing expedited monitoring of unanticipated serious adverse device effects at the time of their occurrence and providing recommendations accordingly
6. Performing quarterly review of all clinical concerns
7. Performing ongoing quarterly review of study progress
8. Reviewing any data that may reflect differences in safety between treatment groups
9. Determining whether study procedures should be changed, or the study should be halted for reasons related to the safety of study participants
10. Performing quarterly review of the completeness and validity of data to be used for analysis of safety and efficacy.

7.5 Data Collection and Database Management

The study will leverage an Electronic Data Capture (EDC) for data collection. Designated full trained site staff will be responsible for handling and entry of all patient-level data into the eCRF as outlined in the protocol. Each eCRF have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. The investigator is responsible for assuring that the data entered into the eCRF is complete, accurate and that the entry and updates are performed in a timely manner.

The EDC system in place will run automatic validation program checks to identify any data discrepancies in the eCRFs for efficient query resolution. In the event that a query is flagged, the system allows for modification and or verification of the entered data by designated staff if needed. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system for prompt review and resolution by site staff.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Additional security measures, data validation steps etc. during and post database lock will be outlined in a Data Management Plan (DMP) which will describe how to handle the data under foreseeable circumstances (e.g., how data will be recorded, tracked, verified for quality control, transferred, and extracted according to FDA guidelines). Along with the DMP, a Data Validation Plan (DVP) containing all edit checks to be performed and the calculations for derived variables are also prepared.

7.6 Quality Control and Quality Assurance

The Sponsor maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control per 21 CFR 820, to ensure compliance with written SOPs as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Sponsor systems are performed by auditors, independent from those involved in conducting, monitoring, or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess 21 CFR 820 and GCP compliance with global and local regulatory requirements, protocols and internal SOPs and are performed according to specified Sponsor processes.

8. STATISTICAL ANALYSIS

8.1 General methodology

Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) and R (R Core Team (2021). R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). Each analysis will be conducted by a blinded statistician, and the statisticians will not confer until QC. The DSMB statistician will be unblinded and generate the randomization schedule. The interim re-estimation of sample size will be conducted by blinded pair programming, as with the main analysis. All personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol deviations, unless otherwise mentioned in the protocol (e.g., DSMB statistician performing randomization and analysis requested by DSMB members).

The statistical analysis plan (SAP) will be approved prior to the interim analysis performed by the blinded independent statistician, and otherwise prior to any lock of the study database and unblinding of the study data. The SAP will provide a detailed description of the statistical methods and expand on the details provided in the protocol.

All data will be presented by treatment group. Descriptive statistics (number of observations, mean, standard deviation [SD], median, interquartile range [q25 and q75], and range [minimum and maximum]) will be provided for continuous variables, and counts and percentages will be presented for categorical variables.

Baseline is defined as the last non-missing measurement before or on the date of first use of the investigational device.

All statistical tests will be 2-sided and performed at the 0.05 level of significance unless stated otherwise. Descriptive analyses and p-values will be presented for exploratory endpoints.

Checks of assumptions (e.g., normality) underlying statistical procedures will be performed and appropriate corrective procedures will be applied (e.g., transformation or nonparametric tests) prior to statistical testing.

8.2 Analysis Populations

For the purposes of analysis, the following analysis sets are defined in Table 4 below.

Table 4. Summary of Analysis Sets

Analysis Set	Description
Enrolled	**All participants who signed the ICF**
Intention-To-Treat (ITT)	**All randomized participants with HAM-D6 measured at baseline. Participants will be included in the ITT population regardless of how often they engage with WB001 or ED001. This analysis set will be the primary set used for analyses/summaries of the primary efficacy endpoint, as well as for all secondary and exploratory efficacy endpoints.**
Per-Protocol (PP)	**All randomized participants also in the ITT population who complete 8 weeks of treatment and have at least 75% compliance on engaging with the Woebot application at least 1 day per week, and who have HAM-D measured at baseline, Week 4, and Week 8, with no other major protocol deviation that could affect the interpretability of the efficacy outcome. This analysis set will be used for sensitivity analyses.**
Safety	**All randomized participants who used WB001 or ED001 and who have at least one post-baseline safety assessment (i.e., C-SSRS). This analysis set will be used for summaries of safety data.**
Note: Inclusion criteria at screening will assess for participants engagement in TAU. If participant is confirmed as not having completed TAU by EOT, the data from these patients will be excluded from the primary analysis; however, their data will be retained for the purpose of conducting exploratory analysis.	

8.3 Sample Size Determination

The concept of a minimally important difference (MID) for depression rating scales are not yet widely established. However, both researchers and a growing number of clinicians who are using measurement-based care employ standardized symptom rating scales to determine whether treatments for depression and other conditions are working effectively (Rush et al., 2021). The degree of symptom improvement that is meaningful

to patients remains unclear. However, a recent analysis based on Brexanolone, an FDA-approved PPD-specific treatment based on HAM-D, provided the first estimates of PPD-specific MID and meaningful change threshold (MCTs) for the HAM-D in this clinically important outcome. It concluded that a 2–3 point change in the HAM-D6 is clinically meaningful and a 4–7 point change is clinically substantial (Rush et al., 2021). A second analysis based on two randomized controlled trials in 482 adult patients with MDD suggested a 2-point difference on the HAM-D6 will allow detection of a change in depression category as mild and moderate and defined as a scores of 8-9 and 10-12, respectively (Ruhe et al., 2005). Thus, as an adjunct to TAU, a 3-point change was identified as an a priori clinically meaningful difference for WB001 to demonstrate a reduction of depression for mild and moderate PPD (for additional justification for use of the HAM-D6 as the primary endpoint see Section 9.1 Primary Endpoint).

[redacted] Simulations using this RCT study data were conducted to determine the power of various sample sizes to detect a 3-point difference in HAM-D6 score between the treatment and control groups at Week 8, controlling for relevant baseline factors and considering potential for additional variability within the study.

[redacted]

9. STATISTICAL METHODS

9.1 Primary Endpoint

The HAM-D is considered the gold standard assessment in clinical trials of major depression, including pharmacotherapy trials in post-partum depression (Hantsoo, et al., 2014). Consequently, as PPD is considered a

subtype of major depression in the DSM-5, the HAM-D was considered the most appropriate primary endpoint. A recent comparative, post hoc analysis of the HAM-D17 and the abbreviated HAM-D6 in the GUIDED trial for MDD treatment found greater sensitivity differences in the treatment effects using the HAM-D6 scale (Dunlap et al., 2019). It was noted that as a multidimensional (or multifactorial) scale the HAM-D17 is good for detecting a broad array of clinical features, it also may reduce the ability to detect change over time, because some factors may not adequately distinguish groups when valid differences exist (Ruhe et al., 2005).

The importance of maximizing signal detection through use of the most sensitive scale to detect treatment effects is of great importance for comparative effectiveness studies. Particularly in a PPD population this provided justification for using the HAM-D6 scale (over the HAM-D17) that more narrowly and precisely measures the "core symptoms" of major depressive disorder according to DSM-5 criteria. The structural validity (unidimensionality) and measurement properties of the HAM-D6 have been well validated (e.g., O'Sullivan et al., 1997; Licht et al., 2005; Bech et al., 2009; Timmerby et al., 2017) and studies comparing the responsiveness of the HAM-D6 and HAM-D17 generally showed that the effect size of treatments was substantially larger according to HAM-D6 versus the HAM-D17 (Timmerby et al., 2017). Further, in studies where symptom reduction was used as an outcome measure, the HAM-D6 detected statistically significant differences between treatment groups more often than HAM-D17 (e.g., Feiger et al., 2006; Bech et al., 2022). Similarly, when remission or relapse rates constituted the outcome measure, HAM-D6 was generally found to be more sensitive than HAM-D17 in detecting differences between treatment groups (e.g., Rasmussen et AL., 2003; Thase et al., 2011).

Thus, for this study, the primary efficacy endpoint is the difference between treatment arms in the HAM-D6 score at Week 8 after controlling for baseline and other covariates. For the ITT population, a restricted maximum likelihood (REML) based linear mixed-effects model for repeated measures (MMRM)-approach will be used to test for systematic differences in change between arms over time, after accounting for participant -specific heterogeneity in HAM-D scores residual error structure. The MMRM will be parameterized to include random effects for site and repeated measures for post-baseline visits using an unstructured residual covariance structure (3 parameters); in the unlikely event that the unstructured covariance matrix fails to converge, the model will be refit with a first order autoregressive covariance matrix (2 parameters).

[redacted]

[redacted]

9.2 Secondary Endpoints

The treatment efficacy of MIBS, EPDS, PHQ-9, and GAD-7 (difference between arms at Week 8, controlling for baseline) will be evaluated using the same analysis plan proposed for the analysis of the primary endpoint (HAM-D). In addition, the differences in HAM-D6 scores between baseline and week 8 within each treatment arm will be calculated. Secondary endpoints are not powered to detect a significant difference between treatment groups and no sequential testing will be applied.

9.3 Exploratory Endpoint(s)

Exploratory analyses will be conducted in the ITT population. Given the ordinal nature of the remaining efficacy endpoints (CGI-I; CGI-S; PGI-C; PGI-S), the analysis plan for HAM-D will be modified to compare treatment arms by the odds selecting a given ordinal category at Week 8 controlling for other factors in the model. Models will be fit via PROC GLIMMIX.

Additionally, the MMRM approach to analyzing the difference between arms will be supplemented via a latent class analysis approach that uses a multiple indicator linear growth model (LGM) for categorical outcomes. More details about the analyses can be found in the SAP.

9.4 Safety Endpoint(s)

AEs and SAEs that may be reported by the participant or detected by the investigator through the C-SSRS will be compared between treatment groups. All safety variables will be summarized descriptively by randomized treatment.

9.5 Analysis of Safety

The Safety Analysis Set will be used for the analysis of AE data.

AEs will be coded with MedDRA. All AEs with an onset date on or after the date of first use of the investigational product and before the date of last use of the investigational device will be collected and presented by system organ class and preferred term in frequency tables. Participants with multiple AEs will be counted only once within each preferred term and system organ class. Key participant information for participants with an AE with an outcome of death, participants with SAEs, and participants with an AE leading to withdrawal from the study will be listed.

9.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be presented descriptively.

9.7 Subgroup Analyses

The study will encourage participant enrollment to be inclusive of all populations as defined by demographic factors such as race, ethnicity, gender identity, age, and by the presence of certain clinical characteristics such as multiple comorbidities. Subgroup analyses will be accounted for by including potential subgroups as covariates in Model 3 (see Section 9.1 Primary Endpoint). [redacted]

9.8 Handling of Missing Values

According to the schedule of events, patients are expected to attend visits at baseline, Week 4, and Week 8. No explicit imputation will be performed; the MMRM model described above will be run on the ITT population, which implicitly imputes missing data under a missing at random (MAR) assumption.

To examine the impact of intermediate missing values and missing values after early withdrawal from the study, sensitivity analyses including multiple imputations will be performed. Missing safety data will not be imputed.

9.9 Interim Analysis

After 50% of the planned participants have completed the study (been evaluated after 8 weeks on treatment) an interim analysis will be conducted on blinded data by an independent statistician to verify that the effect size estimates used to plan the study sample remain reasonable and, if needed, calculate a new required sample given the updated effect size estimates. Specifically, the clinically important difference (CID) analyses (described in section 7.2 of the SAP) will be performed on the interim HAM-D6 data to determine whether clinician judgments of category differences in the HAM-D6 in the context of use of PPD (Δ) are consistent with a priori expectations of a 3-point CID for MDD. Additionally, the SD of the difference between baseline and Week 8 will be calculated to determine whether is it is in line with expectations for detecting a 3-point (or Δ) difference between arms with $\alpha = .05$, two-tailed and $1-\beta = .80$, i.e., n /arm $\geq 2^{*}(z_{\alpha/2} + z_{1-\beta})^{\wedge}2*SD/\Delta = 2*2.8^{\wedge}2*SD/\Delta = 15.68* SD/\Delta$.

9.10 Blinding Analysis

The success of blinding will be assessed at EOT by providing participants with a questionnaire on which treatment arm they believe they were assigned to. Response categories are “active”, “control/placebo”, or “do not know”. Formal analysis will be performed using the James’ Blinding Index (Kolahi et al., 2011), which is a variation of the kappa coefficient that is sensitive not to the degree of agreement but to the degree of disagreement, by placing the highest weight on the “do not know” responses. The index ranges from 0 (total lack of blinding) to 1 (complete blinding). [redacted]

10. ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

This study will be conducted in accordance with the Note for Guidance on GCP ICH Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); US FDA Code of Federal Regulation (CFR) (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the EU Directive 2001/20/EC; the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

10.2 Institutional Review Board

The final study protocol, including the final version of the ICF, must be approved, or given a favorable opinion in writing from the IRBs as appropriate. A written approval from the IRB is required for any study protocol amendment(s), ICF updates, participant recruitment procedures (e.g., advertisements), and any written information to be provided to participants and a statement from IRB to ensure compliance with GCP requirements (if applicable). A current copy of the Investigator's Brochure should be included as part of the written application to the IRB. The investigator is required to sign a protocol signature page confirming his/her/their agreement to conduct the study in accordance with the document and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Sponsor monitors, auditors, Sponsor Quality assurance representatives, designated agents of Sponsor, IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

The IRB approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB approval before the implementation of the changes made to the study, except for changes necessary to eliminate an immediate hazard to the study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of SAEs or other significant safety findings, including adverse drug reactions (both serious and unanticipated), as required by IRB procedures
- Providing oversight of the conduct of the study at the site and adherence to the requirements of all applicable regulations
- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study participants

10.3 Informed Consent

In obtaining and documenting consent via an Electronic Informed Consent Form (eICF), the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the investigator should have the IRB's written approval/favorable opinion of the eICF and any other pertinent information to be provided to participants.

- The investigator or his/her representative will explain the purpose and nature of the study as well as possible AEs to the participant or their legally acceptable representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary, and consent can be withdrawn at any point.
- Participants or their legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of US FDA CFR Title 21 Part 50, local regulations, ICH guidelines, HIPAA requirements in the US, and the IRB or study site.
- Prior to a participant's participation in the study, the eICF should be signed and personally dated by the participant or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion.
- An electronic copy of the signed eICF will be retained at the study site.
- A copy of the eICF and any other pertinent information must be provided to the participant or the participant's legally acceptable representative.
- If the eICF is revised, the revised eICF must have received the IRB's approval/favorable opinion in advance of its use. Participants must be informed of the changes to the eICF and must re-consent to the most current version during their participation in the study if the DSMB confirms the change requires reconsent. The participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information should be documented.

Note: Any study sites that do not have electronic consent capabilities will be permitted to use paper or written copy of the ICF.10.4 Financing and Insurance

Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical study agreement prior to the start of the study, outlining overall Sponsor and investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

Insurance, Indemnity, and Compensation

The sponsor will maintain an appropriate clinical study insurance policy.

Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

11. RECORDS MANAGEMENT

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

Details regarding eCRF access and handling are detailed in the "Electronic Case Report Form Completion and Data Management" section.

During each study visit, a physician participating in the study will maintain progress notes in the participant's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule
- General condition and status remarks by the participant, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the investigator's assessment as to whether the reported AE is related to the investigational device
- Changes (including dosages) in concomitant medications/therapies or procedures
- A general reference to the procedures completed
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the participant via telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF.

Changes to information in the medical record (progress notes) and other source documents are to be initiated and dated on the day the change is made by the investigator (or designee). If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the eCRF will be electronically tracked.

The IQVIA data management department will write a data management plan, which will be finalized prior to performing any data validation.

11.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), central rating results reports, screening logs, completed scales, quality of life questionnaires, and recorded data from automated instruments.

The investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

All source documents from this study are to be maintained by the investigator and made available for inspection by authorized persons. The investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB review, and regulatory inspections. The Sponsor should verify that each participant has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB review, and regulatory inspection.

11.2 Case Report Form Completion and Data Management

An eCRF will be used to store and transmit participant information. The file structure and format for the eCRF will be provided by the Sponsor or its representative and should be handled in accordance with instructions provided.

The eCRF must be reviewed and electronically signed and dated by the investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorized site personnel (e.g., investigators and the study coordinator). The eCRF must be completed as soon as possible (no later than 5 business days) after any participant evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track the changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

11.3 Study Files and Record Retention

All data derived from the study will remain the property of the Sponsor. The Sponsor assumes accountability for actions delegated to other individuals, e.g., the CRO.

Records must be retained in accordance with the current ICH Guidelines on GCP. All essential study documents, including records of participants, source documents, and eCRFs must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of WB001. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the Sponsor. The Sponsor is responsible for informing the investigator when these documents need no longer be retained.

The investigator is not to dispose of any records relevant to this study without written permission from the Sponsor and is to provide the Sponsor the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is participant to inspection by the Sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

12. AUDITING AND MONITORING

Sponsor-assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study, such as assessing participant enrollment, compliance with protocol procedures, completeness and accuracy of data entered into the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The investigator must agree to Sponsor-authorized personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the investigator will assist with the Sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The Sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the Sponsor's contracted CRO(s).

The eCRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Details describing the strategy, responsibilities, and requirements of the study monitoring are provided in the study monitoring plan.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The Sponsor or its representative may conduct audits at the investigative sites including, but not limited to, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. Government regulatory authorities may also inspect the investigator during or after the study. The investigator (or designee) should contact the Sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

12.1 Risk and Quality Tolerance Limits

Perceived risks and quality tolerance limits (QTLs) will be identified and documented before the study start.

The Sponsor will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) will be described in the clinical study report (CSR).

12.2 Protocol Adherence and Deviations

The investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the investigator, site personnel, or the participant.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. For example, important protocol deviations may include enrolling participants in violation of key

eligibility criteria designed to ensure a specific participant population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The investigator should not implement any deviation from the protocol without agreement from the Sponsor and prior review and approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard to a study participant, or when the change involves only logistical or administrative aspects of the study, such as a change in a monitor or telephone number.

In the event of an important protocol deviation, the investigator will discuss the deviation with the Sponsor's medical monitor and will come to an agreement as to whether the participant should be withdrawn from the study due to the important protocol deviation.

13. AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to participant s should be implemented immediately.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB, and the investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

The current version of the ICF will require similar modification if the IRB, investigator, and/or Sponsor, judge the amendment to the protocol to substantially change the study design and/or increase the potential risk to the participant and/or impact the participant's involvement as a study participant. In such cases, the ICF will be renewed for enrolled participants before their continued participation in the study.

14. STUDY REPORT AND PUBLICATIONS

This study will be registered on ClinicalTrials.gov in accordance with applicable laws or publication policy and may also be registered on other publicly accessible websites as necessary.

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with the CSR according to the applicable regulatory requirements. The Sponsor should ensure that the CSR meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

The publication policy of the Sponsor is discussed in the investigator's clinical research agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

15. STUDY START AND TERMINATION

The study start date is the date on which the first participant provides informed consent.

The end of the study is defined as the last participant's last assessment.

Both the Sponsor and the investigator reserve the right to terminate the study or the participation in the study at an investigator's site at any time. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the participants' interests.

If the study is prematurely terminated or suspended for any reason, the Sponsor/investigator/site personnel should promptly inform the study participants and should assure appropriate therapy and follow-up for the participants. Where required by the applicable regulatory requirements, the IRB, DSMB, and other entities involved in the study should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

If the investigator terminates or suspends a study without prior agreement of the Sponsor, the investigator should inform the site personnel. The investigator/site personnel should promptly inform the Sponsor and the IRB. The investigator/site personnel should also provide the Sponsor and the IRB a detailed written explanation of the termination or suspension.

16. CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB personnel, the Sponsor and its authorized representatives are allowed full access to the records.

All study participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, who will be required to give consent for their data to be used as described in the ICF. Participants must be informed that their medical records may be examined by auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Identification of participants and eCRFs shall be by unique participant identification numbers (such as screening or randomization number) only. All personal identifiers according to applicable regulations (e.g., name, phone number) must be redacted permanently by the site personnel and replaced with the participant 's unique identification number in all records and data before transfer to the Sponsor (or designee).

All personal details will be treated as confidential by the investigator and staff at IQVIA.

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Appendix 1: List of Abbreviations

ACOG	**American College of Obstetricians and Gynecologists**
ADL	**Activity of Daily Living**
AE	**Adverse Event**
APA	**American Psychiatric Association**
CBT	**Cognitive Behavioral Therapy**
cCBT	**computerized Cognitive Behavioral Therapy**
CDC	**Centers for Disease Control**
CFR	**Code of Federal Regulations**
CGI-I	**Clinical Global Impression – Improvement**
CGI-S	**Clinical Global Impression – Severity**
CID	**Clinically Important Difference**
CRF	**Case Report Form**
CRO	**Contract Research Organization**
CSQ	**Customer Satisfaction Questionnaire**
CSR	**Clinical Study Report**
C-SSRS	**Columbia Suicide Severity Rating Scale**
CTCAE	**Common Terminology Criteria for Adverse Events**
DMP	**Data Management Plan**

DSM	**Diagnostic and Statistical Manual of Mental Disorders**
DVP	**Data Validation Plan**
eCRF	**electronic Case Report Form**
EOT	**End of Treatment**
EPDS	**Edinburgh Postnatal Depression Scale**
FDA	**Food and Drug Administration**
GAD	**Generalized Anxiety Disorder**
GCP	**Good Clinical Practice**
HAM-D	**Hamilton Rating Scale for Depression**
HIPAA	**Health Insurance Portability and Accountability Act**
IB	**Investigator's Brochure**
ICF	**Informed Consent Form**
ICH	**International Council for Harmonisation**
IPT	**Interpersonal Psychotherapy**
IRB	**Institutional Review Board**
ITT	**Intention-To-Treat**
IXRS	**Interactive Voice/Web Response System**
MID	**Minimally Important Difference**
MCT	**Meaningful Change Threshold**

MDE	**Major Depressive Episode**
MedDRA	**Medical Dictionary for Regulatory Activities**
MIBS	**Mother-to-Infant Bonding Scale**
MMRM	**Multilevel Modeling for Repeated Measures (Mixed Model with Repeated Measures)**
NSR	**Non-Significant Risk**
PGI-C	**Patient Global Impression - Change in Clinical Status**
PGI-S	**Patient Global Impression – Disease Severity**
PHQ-9	**9-item Patient Health Questionnaire**
PI	**Principal Investigator**
PPD	**Postpartum Depression**
PRAMS	**Pregnancy Risk Assessment Monitoring System**
PRN	**pro re nata**
QTL	**Quality Tolerance Limit**
RCT	**Randomized Controlled Trial**
SAE	**Serious Adverse Event**
SaMD	**Software as a Medical Device**
SARS-CoV-2	**Severe Acute Respiratory Syndrome Coronavirus 2**
SAP	**Statistical Analysis Plan**

SCID-5-CT	**Structured Clinical Interview for DSM-5 Clinical Trials Version**
SD	**Standard Deviation**
TAU	**Treatment As Usual**
TRD	**Treatment Resistant Depression**
USADE	**Unanticipated Serious Adverse Device Effect**
USPSTF	**United States Preventive Services Task Force**
WDQ	**Woebot Depression Question**
WHO	**World Health Organizations**

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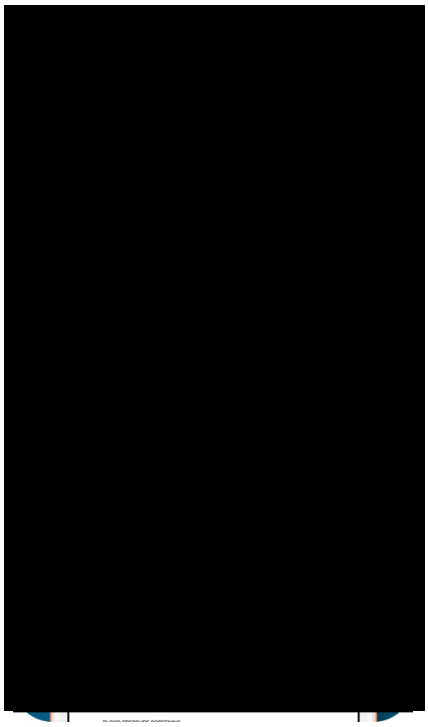

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Appendix 3: Schedule of Events

Mechanism to Execute	Epochs	Screening/Baseline** Day 1 must be completed on same day	Week 4 Day 28 ±3	Week 8 (EOT/ET) Day 56 ±3
Clinical Outcome Assessments			**Intervention Period**	
In-person by site staff	**Randomization** *After the following assessments are completed and patient meets all I/E Criteria	X		
In-person by blinded site staff via tablet or paper copy	**Informed Consent**	X		
In-person by blinded site staff for input in EDC	**Inclusion/Exclusion Criteria**	X		
In-person by blinded site staff for input in EDC	**Demographics**	X		
In-person by blinded site staff for input in EDC	**Previous Medications**	X		
In-person by blinded site staff for input in EDC	**Psychiatric History**	X		
In-person by blinded site staff/PI via tablet	**SCID-5-CT**[a, e]	X		
Hybrid by blinded site staff/PI for input in EDC	**Concomitant Medications and Therapy** *Post randomization, will rely on self-report from participant on continued TAU	X	X	X
Hybrid by blinded site staff/PI for input in EDC	**Pregnancy History and Status** *Post randomization, will rely on self-report from participant on pregnancy status	X	X	X
Virtual by blinded CIR	**HAM-D17**[c] *Primary endpoint is HAM-D 6 derived from HAM-D17	X	X	X

Hybrid by blinded site staff/PI	**C-SSRS**[a] *Safety endpoint and will be administered virtually by PI if safety event is flagged and confirmed	X	X	X
Self-report via link	**EPDS**[b] *If safety flag is raised due to score of >2 on item #10, EPDS, PI/site staff are notified immediately for review, and action, if needed	X	X	X
Self-report via link	**PHQ-9**[b] *If safety flag is raised due to score of ≥2 on item #9, PHQ-9PI/site staff are notified immediately for review and action	X	X	X
Self-report via link	**GAD-7**[b]	X	X	X
Hybrid by blinded site staff/PI into EDC	**CGI-S**[a]	X	X	X
Virtual by blinded site staff/PI into EDC	**CGI-I**[a]		X	X
Self-report via link	**PGI- S**[b]	X	X	X
Self-report via link	**PGI- C**[b]		X	X
Self-report via link	**MIBS**[b]	X	X	X
Self-report via link	**Healthcare Utilization**	X	X	X
Self-report via link	**Program Assignment Assessment (Blinding)**			X
Hybrid by blinded site staff/PI into EDC	**AEs/SAEs Assessment**[a] *Includes confirming no recent hospitalizations for mental health-related incidence	X	X	X
Self-report via link	**CSQ-8**[b]			X
Virtual by blinded PI	**Escalation Trigger Follow-Up**	X [d]		

AE = adverse event; BL = baseline; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; CSQ = Customer Satisfaction Questionnaire; EOT = end of treatment; EPDS = Edinburgh Postnatal Depression Scale; ET= Early Termination visit; GAD = Generalized Anxiety Disorder Questionnaire; HAM-D = Hamilton Depression rating scale; MIBS = Mother-to-Infant Bonding Scale; PHQ = Patient Health Questionnaire; PGI-C = Patient Global Impression of Improvement of Change; PGI-S = Patient Global Impression of Disease Severity; SCID-5-CT = Structured Clinical Interview for DSM-5 - Clinical Trials Version; Hybrid = indicates conducted in-person at BL and virtual by participant post-randomization through link; CIR = Central Independent Rater;

[a] These assessments will be administered by blinded investigator or qualified designee (e.g., sub-investigator, or dually qualified site staff).

[b] These assessments will be self-administered and completed independently by participant s as a link (±3 days of visit date)

[c] Will be administered by a CIR

[d] Any confirmed Escalation trigger through the following three scenarios will result in PI-administered C-SSRS:

- [redacted]

[e] Only includes modules for major depressive disorder (MDD), current and lifetime diagnosis of a psychotic disorder including postpartum psychosis and Schizophrenia, bipolar disorder, homicidal or infanticidal ideation, and history of drug and/or alcohol

AE/SAE collection will begin at the time ICF is signed. AEs/SAEs should be recorded until the EOT visit.

***Note: the HAM-D will be administered as the Structured Interview Guide for the Hamilton Depression Rating Scale – 17 item version (SIGH-D 17-item HAM-D) to derive the HAM-D6 as the primary endpoint**

****Final Screening and Baseline visit assessments must be completed on the same day.**